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FINAL REPORT

(Contract N00014-81-K-0404)

PRESSURE PHYSIOLOGY: STUDIES OF ACUTE AND CHRONIC EXPOSURES TO INCREASED PRESSURES OF OXYGEN AND INERT GASES IN DIVING, DECOMPRESSION AND THERAPY OF DECOMPRESSION AND ISOBARIC GAS LESION DISEASES

TO

OFFICE OF NAVAL RESEARCH

FROM

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This Program of Multiple Projects concerns oxygen tolerance of organ system functions in man. It is the fifth in the series of Institute national collaborative Predictive Studies (PS V), concerned with defining effects upon specific human organs or systems of extremes of respiratory and pressure environments, with relevance to medicine and human function in unusual circumstances. The Program involves multiple investigators who concurrently conduct different but correlated component projects, in a completely integrated program within each single experiment exposure. It follows over ten years of prior animal and human studies.

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The Program is based upon recognition that oxygen, at essentially all pressures, combines useful effects critical to prevention and relief of hypoxia, with undefined and potentially serious toxic effects which now limit oxygen use. It recognizes also that opportunity now exists to define and then improve tolerance to oxygen at normal and higher oxygen pressures, with prospects for large improvements in general therapeutic hyperoxygenation, in undersea activity and in aerospace operations.

The overall objective is to measure the time courses of onset and reversal of effects produced during continuous hyperoxia upon central nervous system, pulmonary, cardiac and other critical functions. The program conception and overall design is based upon hypotheses that: (a) Rate of onset of a specific oxygen poisoning effect is different in time course from rate of recovery (since processes involved are different). (b) Rate of development of toxic effects will be different in different organs and at different oxygen pressures. (c) Oxygen effects will be detectable in organ systems prior to onset of convulsions. (d) Rate of recovery will be related to degree of toxic effect. (e) Rates of recovery will differ for exposures to different oxygen pressures.

Conditions of continuous O2 exposures are at sedentary rest, for approved maximum conditions of: 3.0 ATA - 3.5 hrs, 2.5 ATA - 6 hrs, 2.0 ATA - 12 hrs, 1.5 ATA - 18 hrs, with 0.2 ATA controls and termination in event of significant effect.

The range of 1.5, 2.0, 2.5 and 3.0 ATA was selected because information concerning human pulmonary hyperbaric oxygen poisoning is available only at 2.0 ATA, and essentially no information exists for rates of central nervous system, heart or any other organ system at any of these oxygen pressures. Nevertheless, this range is important in medicine, undersea activity and therapy of gas lesion diseases in all states.

Sufficient numbers of subjects (7-18) are used at each pressure for appropriate statistical analysis. Concurrent measurements of oxygen effects are made on pulmonary, cardiac and specific nervous system functions. For measurement of changes in neurosensory and brain function, monitoring of electroencephalographic activity and intermittent visual and auditory evoked cortical electrical responses is accompanied by repeated measurements of perceptual, cognitive, and psychomotor function. Visual functions are monitored by repeated measurements of visual acuity, visual fields, accomodation, pupil size, color vision, electroretinography. Auditory function is measured by pure tone air conduction determinations of hearing thresholds. Vestibular reactivity is tested pre- and post-exposure by caloric stimulation.

Measurements of pulmonary function include forced expiratory and inspiratory vital capacities and peak flow rates, slow vital capacity, static lung volumes (inspiratory volume, inspiratory and expiratory reserve volume, residual volume, functional residual capacity, total lung capacity), closing volumes, carbon monoxide diffusing capacity, alveolar-arterial PO_2 and PCO_2 values, static and dynamic lung compliance, airway resistance, air vs. HeO_2 expiratory flow rates, and cell characteristics in bronchopulmonary lavage.

TABLE OF CONTENTS

PAGE NUMBERS

PRINCIPAL INVESTIGATOR: Lambertsen, C.J. 147-03-8085

C. ABSTRACT SECTION

ORGANIZATION: TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA
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TITLE OF PROPOSAL:

"DEFINITION AND EXTENSION OF OXYGEN TOLERANCE IN MAN"
(PREDICTIVE STUDIES V)

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ABSTRACT

This Program of Multiple Projects concerns oxygen tolerance of organ system functions in man. It is the fifth in the series of Institute national collaborative Predictive Studies (PS V), concerned with defining effects upon specific human organs or systems of extremes of respiratory and pressure environments, with relevance to medicine and human function in unusual circumstances. The Program involves multiple investigators who concurrently conduct different but correlated component projects, in a completely integrated program within each single experiment exposure. It follows over ten years of prior animal and human studies.

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D. WORK PLAN

1. SPECIFIC AIMS

Aims

The integrated research encompassed by Predictive Study V and the planned Predictive Study VI overall work plan represents continuation of a major collaborative investigative Program. This program has been planned and prepared for by over six years of preliminary research in animals. It encompasses multiple correlated projects and multiple conditions of oxygen exposure. The overall goal of Predictive Study V is determination of safe limits of oxygen tolerance (to oxygen poisoning) for specific vital organs and critical functions in normal man, during continuous exposure to each of several levels of increased inspired oxygen pressure. This aim is directed to the use of the measurements to construct oxygen tolerance tables and diagrams as guides for rational operational and medical therapeutic use of continuous periods of hyperbaric oxygen exposure.

The second major aim in determinations of tolerance to continuous O_2 exposure is to provide the necessary baseline information for optimal extension of human organ oxygen tolerance in Predictive Study VI (investigation of oxygen tolerance extension by programmed interruption of oxygen exposures over the full range of useful oxygen pressures). Results of the continuous oxygen exposures will also aid in identification of sensitive indices of oxygen effects on specific organs and functions that will later be used to quantitate extension of oxygen tolerance in the planned interrupted exposures of Predictive Study VI.

Together the aims of this Program are fundamental to advance in medical hyperoxygenation including 1.0, 1.5, 2.0, 2.5 and 3.0 ATA and undersea/aerospace activity.

Scope of Proposed Further Work

At this Phase of the overall Predictive Study V Program, continuous human subject exposures to oxygen have been carried out for determination of specific organ and function tolerance to the oxygen pressures of 3.0, 2.0, and 1.5 ATA. A series of 24-hour, 1.0 ATA air control exposures will be performed before the end of the current program year, using a subgroup of the subjects who were exposed to oxygen at 1.5 or 2.0 ATA.

Analysis of the data from the oxygen exposures at 3.0, 2.0, and 1.5 ATA is in progress and will be continued into the next year. Detailed examination of results obtained at each pressure is being performed to identify onset times, rates of development, and magnitudes of oxygen effects on specific organs and functions. Significant organ and function deficits which are found at 3.0, 2.0, and 1.5 ATA will be compared to identify differences

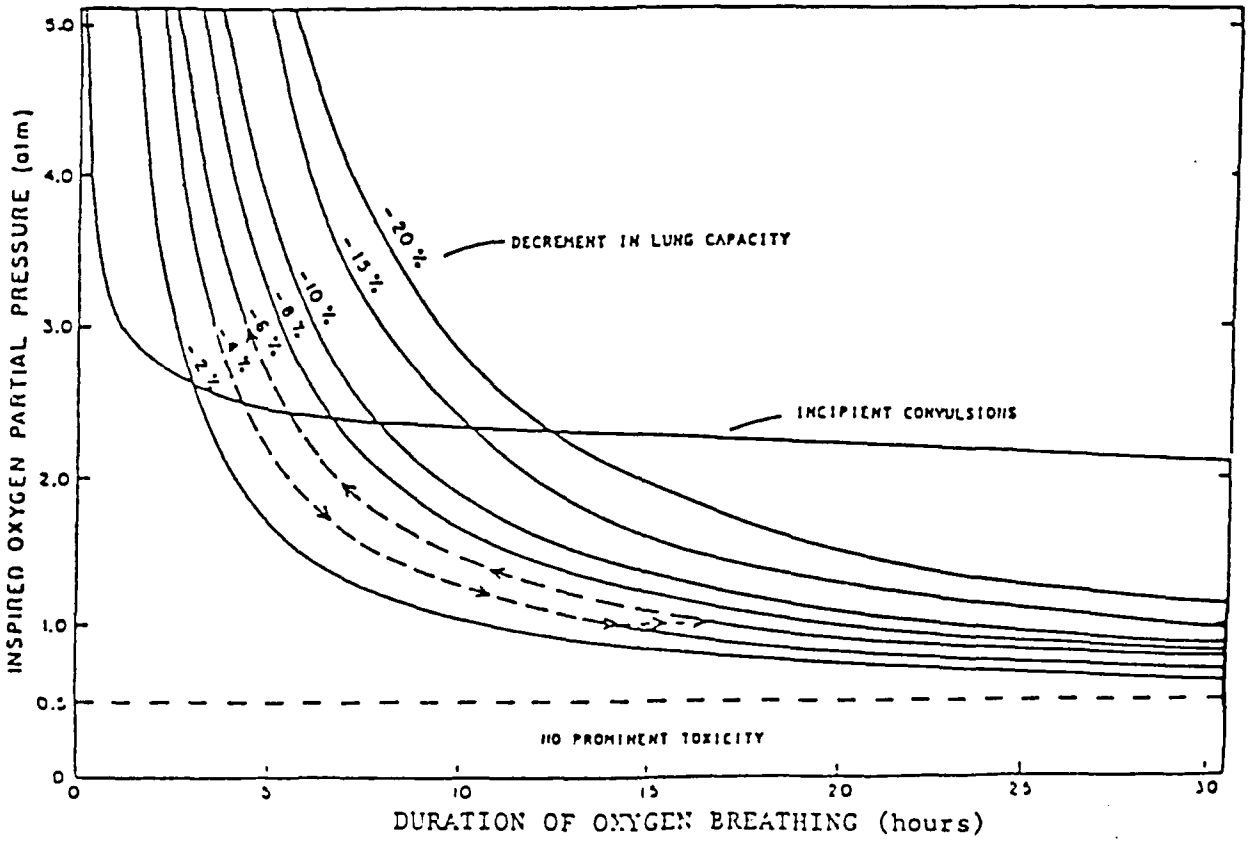
in sequences of occurrence and final magnitudes of effects at each pressure. Additional experiments will be conducted as necessary to clarify data. This analysis and integration will be required prior to performance of the critical 2.5 ATA exposure series, in order to sharpen the experiment design of the planned final series of continuous oxygen exposures by using the detailed information that the Program is now providing for oxygen pressures both above and below 2.5 ATA. The 2.5 ATA exposure series is critical because both our previous predictive curves (Fig. 1) and recent experiment results indicate that tolerance to oxygen at 2.5 ATA will be limited by concurrent development of CNS and pulmonary effects. Following completion of the 2.5 ATA phase of investigation, the new data will be incorporated into an overall analysis and integration of data obtained at the oxygen pressures of 1.5, 2.0, 2.5, and 3.0 ATA.

FIGURE 1.

OXYGEN TOLERANCE IN MAN

PROGRESSION OF PULMONARY OXYGEN TOXICITY DURING

CONTINUOUS EXPOSURE TO VARYING PARTIAL PRESSURES OF OXYGEN



The next two years will constitute a period of transition from the final Phase of Predictive Study V (definition of oxygen tolerance during continuous oxygen exposure) to the initial Phase of Predictive Study VI (extension of oxygen tolerance by intermittent oxygen exposure). Major objectives for this period include: overall analysis and integration of the data obtained during continuous oxygen exposures, as described above; development of oxygen tolerance tables for effects of continuous oxygen exposure on specific organs and functions; completion of the design for the initial studies of CNS, pulmonary, and cardiac oxygen tolerance extension by intermittent oxygen exposure; and performance of the first group of intermittent oxygen exposure profiles.

Milestones

Within the overall Predictive Study Program concerning human oxygen tolerance, several types of milestone can be characterized.

One type is characterized by quantitative definition of oxygen effects on specific organs and functions during continuous exposure to a particular level of respired oxygen pressure (e.g. 3.0 ATA) in man at rest. The resting state is intentionally employed to provide for determination of maximum tolerance as the necessary baseline for related examination of modifying factors [e.g. EDU Study of O_2 tolerance in underwater exercise (1); subsequent IFEM studies of intermittent exposure]. Verification that critical organ systems and functions are not affected during tolerable exposure durations is just as important as quantitation of effects that occur.

Another type of milestone relates to the definition of comparable functional decrements over a selected range of different oxygen exposure pressures (e.g. 1.5, 2.0, 2.5, and 3.0 ATA).

Yet another pair of milestones is characterized by quantitative descriptions of oxygen tolerance extension by specific patterns of interrupted oxygen exposure at a particular pressure and over a selected range of pressures.

All of the characterized types of milestones are interrelated, because new information obtained at one oxygen pressure affects the design and performance of experiments at other pressures. Similar inter-relationships exist for information obtained during continuous and interrupted oxygen exposures. Upon beginning investigation at each oxygen pressure, the preliminary design based on results obtained at other pressures is further refined by the performance of a few pilot studies. In addition to sharpening experiment design, the pilot studies provide opportunities for investigator training, instrumentation revision, and adaptation of procedures.

Specific milestones planned for the next 3-year Program period are as follows:

Fiscal Year	Specific Milestones and Scope
1986	Analysis and Integration of Results from 3.0, 2.0, and 1.5 ATA Oxygen Exposure Series.
	Design of 2.5 ATA Oxygen Exposure Series based on Integrated Analysis of Completed Series. Pilot studies and performance of eight Subject Exposures at 2.5 ATA PO_2 for six hours.
	Analysis of Data from 2.5 ATA Series and Incorporation into Overall Integrated Analysis of Continuous Oxygen Exposure at 1.5, 2.0, 2.5, and 3.0 ATA.
1987	Completion of Design for Initial Studies of CNS, Pulmonary, and Cardiac Oxygen Tolerance Extension by Intermittent Oxygen Exposure. (Based extensively on prior experiments in animals.)
	Performance of two Intermittent Oxygen Exposure Profiles at 2.0 ATA with eight Subject Exposures in each Profile.
	Analysis of Data from Human Intermittent Oxygen Exposures and Comparison with Available Data from Animal Intermittent Exposures for Determination of Similarities and Differences in Patterns of Response.
1988	Analysis and Integration of Available Data from Human and Animal Intermittent Oxygen Exposures.
	Completion of Design for Human Studies of CNS, Pulmonary, and Cardiac Oxygen Tolerance Extension at 2.5 and 3.0 ATA. (Based on prior experiments in animals.)
	Performance of two Intermittent Oxygen Exposure Profiles at 2.5 ATA with eight Subject Exposures in each Profile.
	Performance of Pilot Studies of Intermittent Oxygen Exposure Profile at 3.0 ATA with eight Subject Exposures.
	Analysis and Integration of Results from Human Intermittent Oxygen Exposures at 2.0, 2.5, and 3.0 ATA.

2. SCIENTIFIC SIGNIFICANCE

Background

The fundamental goals of the Predictive Studies Program for Oxygen Tolerance Definition in man have been clearly recognized by IFEM and several national agencies as having exceptional scientific and practical significance to development of medical therapy, undersea operations, and manned aerospace activity. This exceptional significance derives from the multiple roles and effects of oxygen itself in biological processes, generation of pulmonary and eye disease, medical therapy, and operational procedures of diving and decompression. Postponement for many years in execution of the Program has been related to the need for extensive basic information concerning mechanisms and chemical sites of action of oxygen poisoning, and to the difficulties in attracting the multi-disciplinary staff required for a comprehensive investigative effort in man, beyond the capability of any one laboratory. The Program for continuous oxygen exposure has been designated the Fifth in the important Series of Predictive Studies, involving collaboration of federal and university organizations to serve national purpose. Investigation of oxygen tolerance extension by programmed interruption of exposure is designated Predictive Study VI.

Uniqueness of Oxygen. Oxygen is unique in that its broad importance in diving, and its basic importance to the preservation of life in disease, coexist with universally toxic properties. These toxic effects, at sufficient pressure and duration of oxygen exposure, will ultimately disrupt or destroy the vital processes of essentially any cell. The balance between life-sustaining and destructive properties of oxygen is maintained in part by intrinsic cellular antioxidant defense mechanisms that have evolved in eons of adaptation to atmospheric oxygen tensions (2,3). Because of this balance, pure oxygen or high partial pressure of oxygen in nitrogen or helium diving mixtures can be breathed for usefully long periods at one and more atmospheres ambient pressure. The extent and safety of the practical application of this ability to use oxygen at high pressures, and hence the further improvement of operational methods, depends upon clear demonstration of rate of development of adverse effects of oxygen on critical body functions (4).

Limitations on Oxygen Use in Therapy, Diving, Decompression, and Aerospace Activity

Degree and Duration of Oxygen Exposure. The toxic chemical effects of high oxygen pressures, exerted upon and inactivating multiple cellular and membrane enzyme systems, increase progressively in degree as duration of exposure to high oxygen pressure lengthens. The rate of enzyme inactivation, with consequent failure of cell and organ function, is speeded progressively as the oxygen partial pressure of an exposure is increased. If all cells and all different enzymes were both a) equally sensitive to

oxygen toxicity, and b) exposed in the body to the same partial pressures of oxygen, prediction of oxygen tolerance would be relatively simple. In actual fact, each enzyme has its own susceptibility to oxygen poisoning. Moreover, the same enzyme in different cell forms (brain, lung, liver) has a different cellular environment and different level of exposure to oxygen (4). Finally, the enzymatic composition of cells in different vital organs is not uniform. For all these reasons, the detectable consequence of cellular poisoning is grossly different, organ-by-organ (brain, skin, bone, lung, eye, muscle) (4).

Because of the expected gross difference in the degree, order of involvement, and character of oxygen poisoning at low and high levels of hyperoxia, it is necessary to determine the rate of development of oxygen toxicity at several oxygen pressures on organ systems critical to performance and survival.

Functions of Predictive Study Programs

For many decades, against the background of expanding basic information concerning oxygen toxicity in animals, there had remained essentially complete unawareness of the rates of development of specific neurological dysfunctions during human hyperoxic exposure. The present Program to develop oxygen tolerance limits in man was intended to obtain quantitative, dose-effect information in normal men, concerning pre-convulsive influences of oxygen on organ and system functions not previously investigated in detail, over a range of oxygen pressures in which quantitative measurements of oxygen effect on human organ function were lacking. The program has partially accomplished its goals. Selection of indices of effect for study in man has been based upon information and concept derived in the Institute's extensive research concerning patho-physiologic mechanisms of oxygen poisoning in tissues, organs and animals.

Relation to Existing Information on Neurological and Pulmonary Oxygen Tolerance

In prior oxygen-related research, this Institute performed detailed measurements in man of oxygen effects upon brain metabolic function (9), and of the interacting effects of carbon dioxide and oxygen on brain oxygen tension. It also determined the rate of development of human pulmonary oxygen poisoning at 2.0 ATA, and analyzed existing other studies to a) construct "Pulmonary Oxygen Tolerance Curves" (5), and b) provide the concept of a "Unit Pulmonary Toxic Oxygen Dose" (UPTD) (6).

Prior to the initiation of the current Program, no quantitative information relating to rate of development of Pulmonary oxygen poisoning in man existed for oxygen pressures greater than 2.0 ATA (Fig. 2A), and no quantitative information existed for Central Nervous System oxygen poisoning in man at pressures greater than 1.0 ATA (Fig. 2B). This was true over the

many years in which hyperoxic therapy of decompression diseases and other disorders was extensively used. At the present stage of the overall program extensive information has been obtained which will be analyzed and supplemented during the coming year.

Fig. 2a PULMONARY OXYGEN TOLERANCE IN MAN

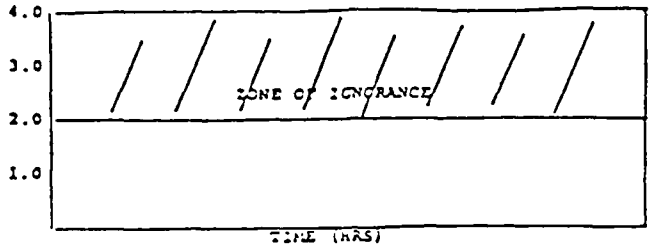
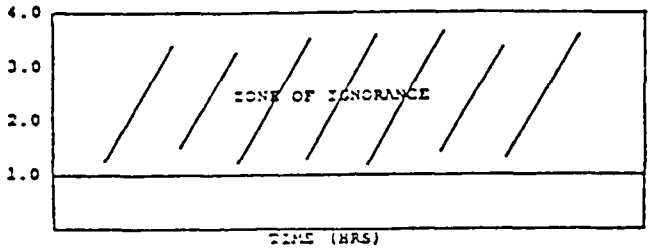


Fig. 2b CENTRAL NERVOUS SYSTEM OXYGEN TOLERANCE IN MAN



Information concerning oxygen tolerance limits for Central Nervous System functions has great importance in hyperbaric therapy and in forms of diving, where onset of convulsions and unconsciousness will result in incapacitation and death. Following the general descriptive information obtained in many human exposures by Donald (7) and Yarbrough et al (8) during World War II, no systematic study of the characteristics of central nervous system oxygen poisoning in man was performed. The important observation by Behnke et al (11) that human visual function is grossly reduced during prolonged exposure to oxygen at 3.0 ATA had not (until initiation of this Program) been adequately followed-up in man except at 1.0 ATA, in spite of a clear indication of a prominent effect upon a critical central nervous system function.

One difficulty, persistent over several decades, has been a preoccupation with oxygen-induced convulsions in animals, rather than with measurements aimed at the subtle central nervous system changes which may be detectable in man prior to convulsions. In this laboratory oxygen convulsions are considered a signal of spreading electrical disruption resulting from cumulative effects of oxygen toxicity, rather than representing the onset of oxygen toxicity (4). The present Predictive Study V concerns the pre-convulsive effects of oxygen and does not involve intentional generation of convulsions.

Philosophy of Institute Overall Oxygen Tolerance Program

A key concept generated early in this Institute's continuing Oxygen Research Program is that, following a toxic exposure to hyperoxia, a sufficient interval of normoxia will allow for recovery and permit useful hyperoxic exposure again. The duration of the recovery interval required will depend upon the rate of onset, nature and degree of induced poisoning (and hence upon the rate of recovery). By systematic investigation of rates of poisoning of different functions or systems, at different oxygen exposure pressures (ATA PO_2), with tracking as practical of the rates of recovery, it should be possible to define a) tolerance of critical functions to oxygen, and b) optimal programs of intermittent oxygen exposure, allowing maximum effective use of oxygen at various pressures important to therapy and undersea operations, from one to several atmospheres. These concepts, summarized in part by Table 1, form the bases for the animal and human investigations underlying the correlated Programs of the current Predictive Study V and the planned Predictive Study VI.

TABLE 1

PROGRAM CONCEPTS OF OXYGEN TOLERANCE AND ITS EXTENSION

Oxygen is a universal poison. Its effect must be expressed in all vital functions.

The rate and degree of oxygen poisoning development are proportional to oxygen dose, and determined by interactions between oxygen dose and individual tissue susceptibility.

The rate and degree of oxygen poisoning development can be predictably diminished by systematic interruption of oxygen exposure.

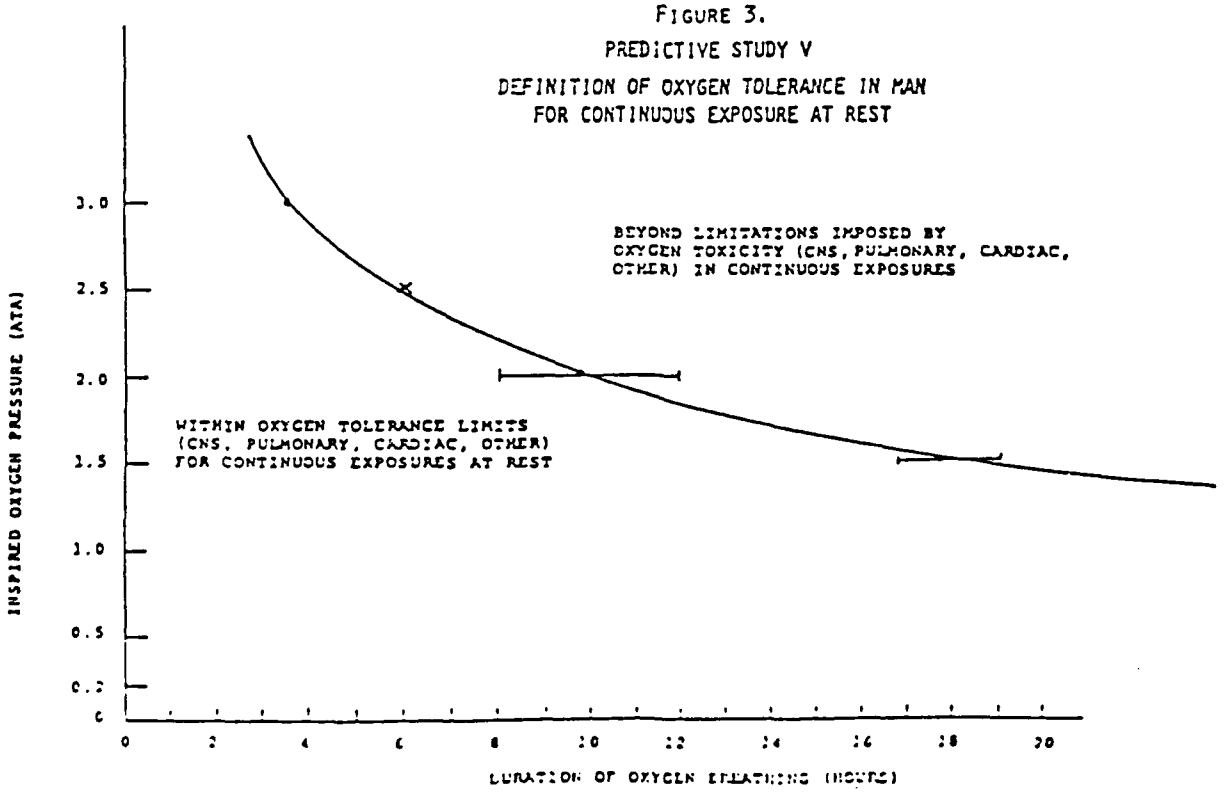
The rate of recovery from oxygen poisoning is essentially unknown in any tissue.

The rate of recovery from systemic oxygen toxicity is a complex of individual recovery rates from discrete enzymatic and other chemical targets.

The rate of recovery from oxygen poisoning is slower from severe poisoning than from mild toxicity.

In contrast to the wide zones of ignorance (Figs. 2A and 2B) that existed prior to initiation of Predictive Study V, the state of oxygen tolerance information at the present Phase of the overall Program is described in Fig. 3. The solid point at 3.0 ATA - 3.5 hours indicates that 14 resting subjects were able to complete the full 3.5-hour exposure. One additional subject convulsed at 3.0 hours (ref. 1984 Report), and another was taken off O_2 at 2.5 hours just before loss of consciousness for about 30 seconds in association with extreme bradycardia (ref. 1983 Report). The points at 2.0 and 1.5 ATA represent average exposure durations of 9.7 hours in seven subjects and 17.7 hours in nine subjects, respectively, with corresponding ranges of 8.0 to 11.9 hours and 16.8 to 19.0 hours. The point at 2.5 ATA - 6.0 hours (X) indicates the approved duration for 2.5 ATA oxygen exposures that will be performed during the next year. Within the area to the left of the smooth curve shown, specific information regarding tolerance of the central nervous system, lung, heart, and other vital organs to continuous oxygen exposure has now been made available. This data base will be further expanded and integrated during the final Phase of Predictive Study V (Continuous O_2 Exposure). The area to the right of the curve is clearly beyond the limitations imposed by tolerance to <u>continuous</u> oxygen exposure for one or more vital organs at each pressure. The primary goal of Predictive Study VI is to use systematic interruption of oxygen exposure *as a means for* extending overall and specific organ oxygen tolerance as far to the right of the limits for continuous exposure as is both possible and practical.

FIGURE 3.
PREDICTIVE STUDY V
DEFINITION OF OXYGEN TOLERANCE IN MAN
FOR CONTINUOUS EXPOSURE AT REST



3. PROGRESS REPORT

Period: 1 January 1985 to 31 December 1985.

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W.H. Cobbs, M.D. Assistant Professor of Neurology
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15%

PROGRESS REPORT (Continued): Studies at 3.0, 2.0 and 1.5 ATA

Summary of Goals of Original Program

The initial Goal of the Program, and still primary, was the "Definition of Oxygen Tolerance in Man," under conditions of oxygen pressure relevant to the multiple applications of hyperoxia in undersea operations, and in the prevention and therapy of decompression sickness. Specific aims included quantitative measurement of rates of development of oxygen effect upon selected central nervous system and other neural functions, correlated with measurements of important functions of lung and other critical organs or systems (e.g. eye, ear, heart, muscle).

The initial Phase of the Program focused on continuous oxygen breathing at 3.0 ATA where neural effects are dominant and limit the safe duration of exposure. Although the present investigation of continuous oxygen exposure at 2.0 and 1.5 ATA confirmed, as expected, that pulmonary effects are dominant at these pressures, important visual deficits were found in a few subjects. It is equally important to document the absence of subtle objective neural effects under exposure conditions in which there are no obvious symptomatic manifestations of cerebral oxygen poisoning.

The Goals for comprehensive measurement of oxygen effect, and development of predictive oxygen tolerance tables remain unchanged. The presently approved pattern of oxygen exposure durations at the several exposure pressures is as follows:

Planned Pressures and Maximum Durations of Continuous Oxygen Exposures

Ambient Pressure (ATA)	PO_2 (ATA)	Duration (Hrs)
1.0	0.21	24
1.5	1.50	24
2.0	2.00	12
2.5	2.50	6
3.0	3.00	3.5

Overall Progress in the Program

During the initial Phase of Predictive Study V, 18 subject exposures to oxygen at 3.5 ATA for 2.0 to 3.5 hours were performed. Although results of preliminary analysis were reported previously (1983 and 1984 Reports), detailed analysis of the large volume of data is still in progress and will continue into the next year of the Program. Correlation and integration of the 3.0 ATA data with results from other pressures will also continue throughout the final Phase of Predictive Study V. The

experiment profile (Fig. 4) and measurement module (Fig. 5) employed in the 3.0 ATA oxygen exposures are included here to facilitate comparison with the longer exposures and expanded measurement module used in the present Phase of the Program.

Following pilot exposures, a total of 17 subject exposures to oxygen at either 2.0 or 1.5 ATA were performed during the past 7 months of investigation (Table 2). Subjects were studied in pairs for all exposures except one. Preparation for the 2.0 and 1.5 ATA oxygen exposures included adaptation of the 3.5 ATA measurement module to incorporate additional organ function components with increased emphasis on pulmonary function, alteration of experiment design to accommodate longer exposures and multiday recovery periods, modification and improvement of instrumentation and methods, training of investigators in performance of new procedures separately and as part of an expanded measurement module, and reassurance that subject safety was not compromised at any point during oxygen exposure or recovery.

TABLE 2

SUBJECT EXPOSURES AT 2.0 AND 1.5 ATA PO_2

Subject	Oxygen Pressure (ATA)	Exposure Duration (Hours)
R.O.	2.0	11.9
J.S.	2.0	10.8
C.H.	2.0	8.0
P.F.	2.0	8.2
S.A.	2.0	10.5
R.C.	2.0	9.0
R.L.	2.0	9.7
Mean		9.73
C.C.	1.5	3.0
B.K	1.5	17.0
G.L.	1.5	17.0
M.M.	1.5	17.7
C.S	1.5	17.0
J.U.	1.5	18.1
J.M.	1.5	16.8
D.M.	1.5	18.8
S.J.	1.5	17.9
J.C.	1.5	19.0
Mean (omit C.C.)		17.65

Figure 4.

PREDICTIVE STUDIES V EXPERIMENT PROFILE
(3.0 ATA)

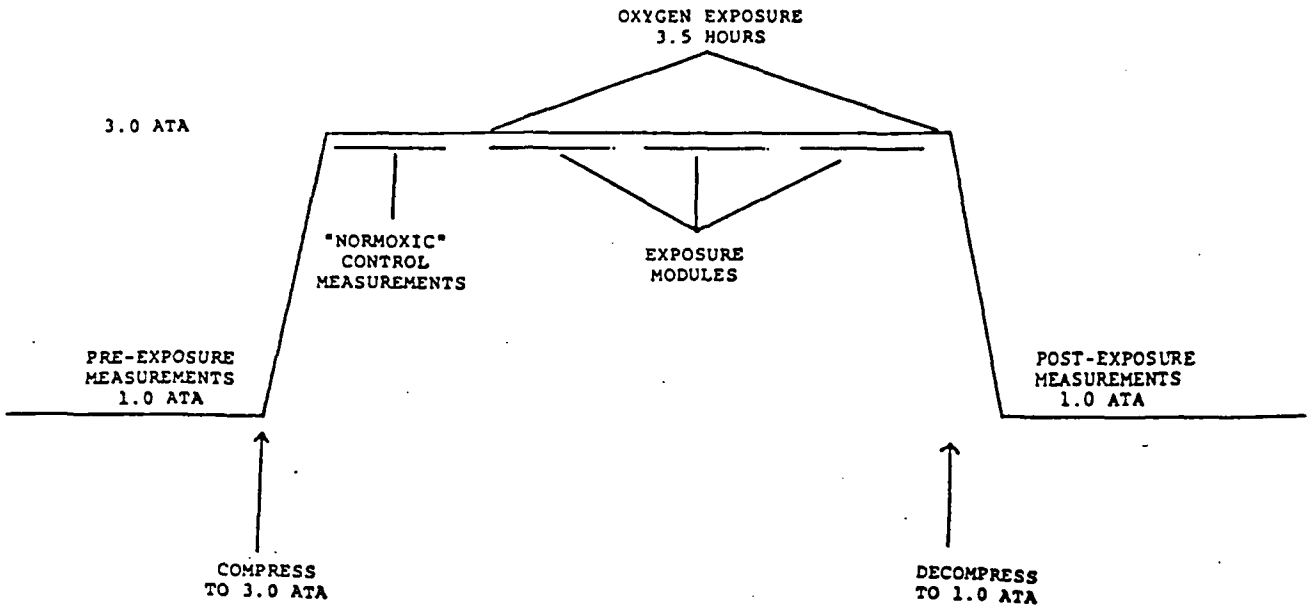
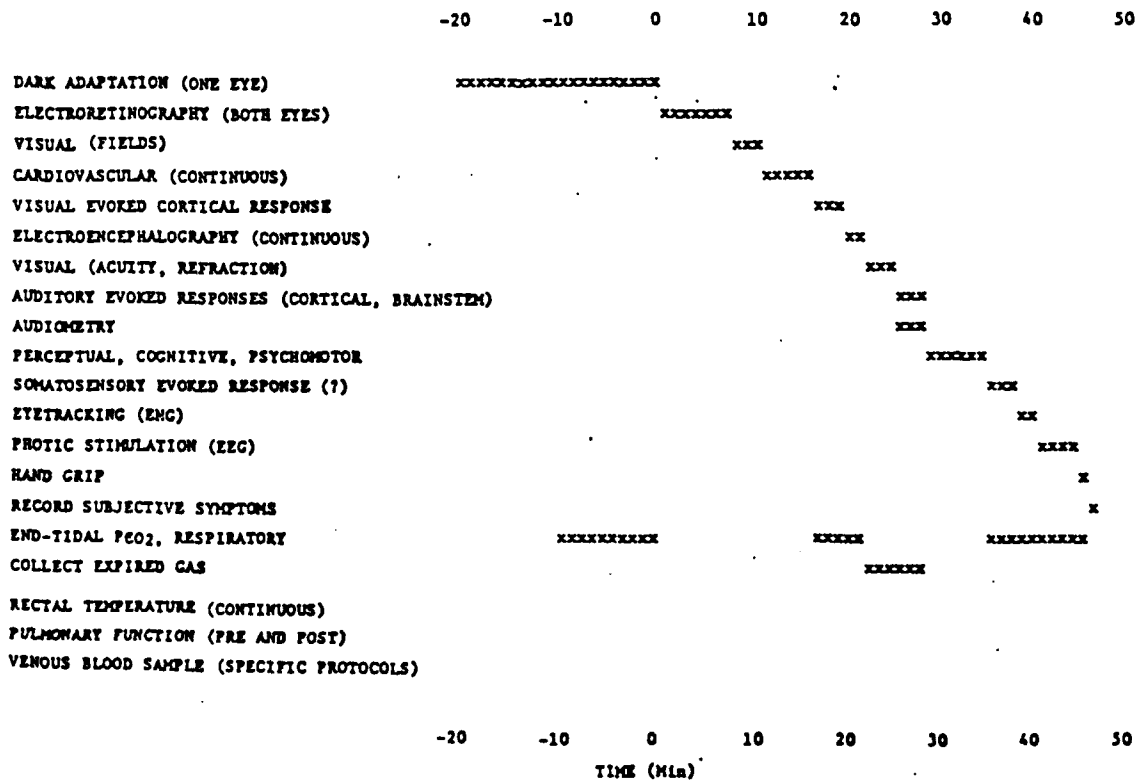


FIGURE 5.

PREDICTIVE STUDIES V
CENTRAL NERVOUS SYSTEM OXYGEN TOLERANCE IN MAN
MEASUREMENT MODULE
(3.0 ATA)



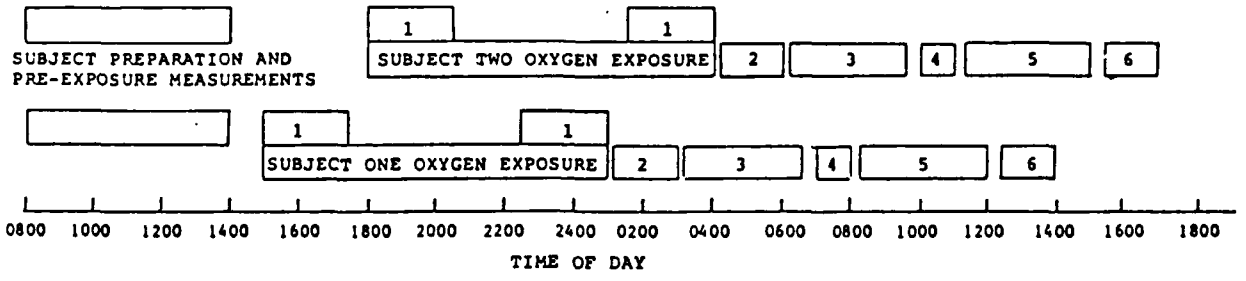
The experiment sequence used for each pair of subjects at 2.0 ATA is shown in Fig. 6. Pre-exposure control measurements were obtained within several hours before the start of oxygen breathing for some parameters and on a previous day for others. In order to provide time for directing attention to one subject at a time during performance of a 2.5-hour measurement module (Fig. 7) at the start and end of each exposure, the periods of oxygen breathing were staggered for the two subjects. Post-exposure measurements that focused primarily on central nervous system and pulmonary function were performed during the initial 12 to 14 hours of the recovery period. Follow-up measurements were continued for one or more weeks, if necessary, until all functions returned to the normal range.

The experiment sequence used for each subject pair at 1.5 ATA is shown in Fig. 8. In addition to the 2.5-hour measurement modules (Fig. 7) during the earliest and latest hours of oxygen breathing, the longer exposure duration at 1.5 ATA permitted periodic monitoring of CNS and pulmonary function. Sequences of early post-exposure and follow-up measurements were similar to those used after the 2.0 ATA exposures.

FIGURE 6.

PREDICTIVE STUDY V EXPERIMENT SEQUENCE
2.0 ATA SERIES

1. COMPLETE MODULE (FIG. 7)
2. BLOOD CHEMISTRY, ARTERIAL BLOOD GASES, EFFECTIVE DIFFUSING AREA
3. COMPLETE PULMONARY FUNCTION
4. BRONCHOALVEOLAR LAVAGE
5. AUDITORY-VESTIBULAR EVALUATION, AUDITORY BRAINSTEM RESPONSE
6. PARTIAL PULMONARY FUNCTION



Preliminary analysis of selected data components from the 2.0 and 1.5 ATA oxygen exposure series are available for inclusion in this Report. As stated previously for the 3.0 ATA series, complete processing and analysis of the data obtained before, during, and after oxygen exposure at 2.0 and 1.5 ATA will require additional months of effort. A series of 20-hour, 1.0 ATA, air breathing control exposures will be performed later this year.

FIGURE 7.

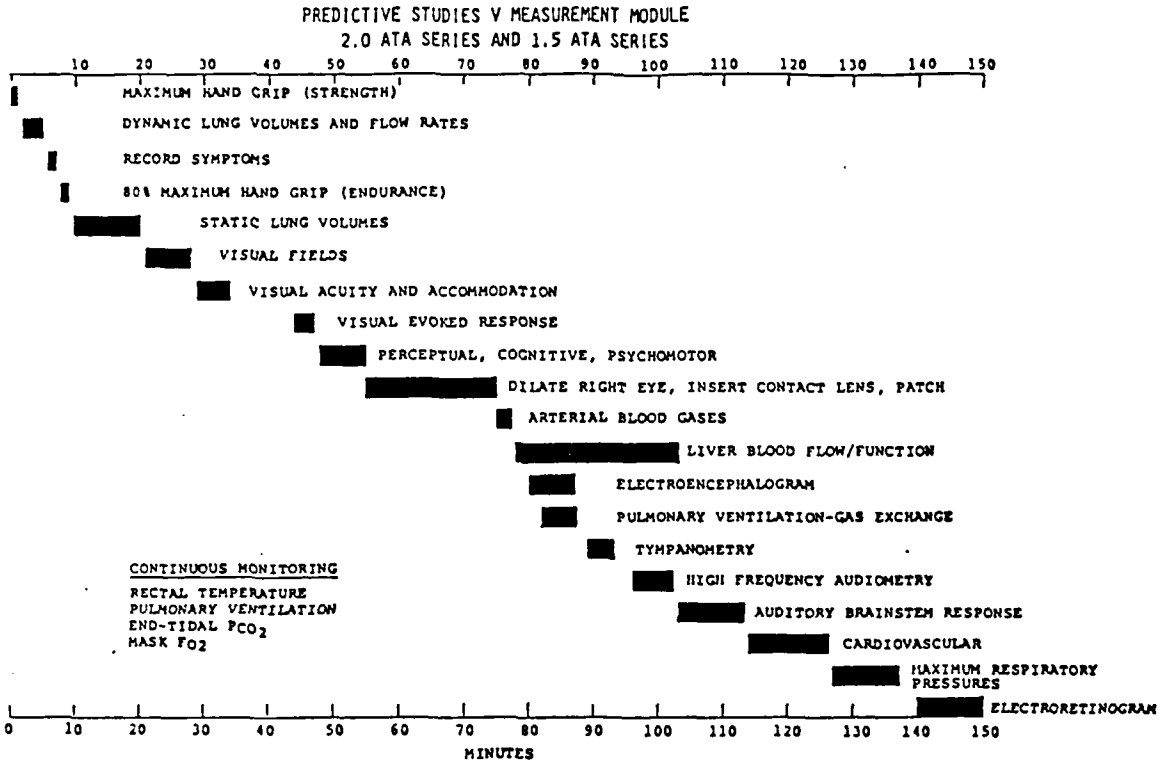
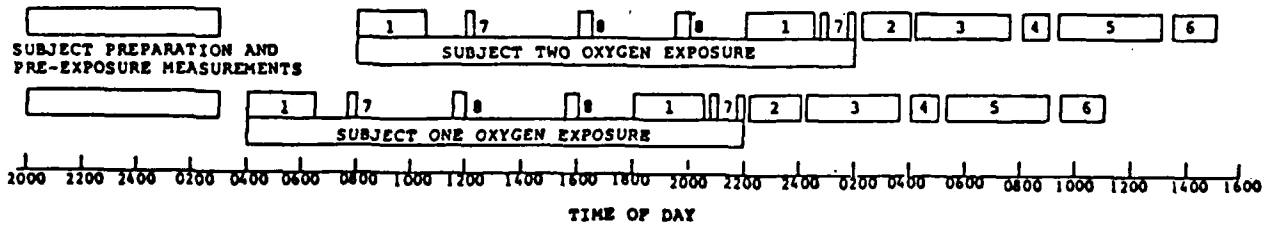


FIGURE 8.

PREDICTIVE STUDY V EXPERIMENT SEQUENCE
1.5 ATA SERIES

1. COMPLETE MODULE (FIG. 7)
2. BLOOD CHEMISTRY, ARTERIAL BLOOD GASES, EFFECTIVE DIFFUSING AREA, CONTROL OF VENTILATION
3. COMPLETE PULMONARY FUNCTION
4. BRONCHOALVEOLAR LAVAGE
5. AUDITORY-VESTIBULAR EVALUATION, AUDITORY BRAINSTEM RESPONSE
6. PARTIAL PULMONARY FUNCTION
7. DYNAMIC LUNG VOLUMES AND FLOW RATES, STATIC LUNG VOLUMES
8. DYNAMIC LUNG VOLUMES AND FLOW RATES, STATIC LUNG VOLUMES, ELECTROENCEPHALOGRAM, PULMONARY VENTILATION-GAS EXCHANGE



RESULTS OBTAINED IN CURRENT PROGRAM YEAR

Background - General Experiment Procedure

Subject Evaluation and Training. Each subject candidate received a comprehensive medical evaluation that included a history and physical examination, detailed neurological examination, electrocardiogram, chest x-ray, hematology profile, urinalysis, electroencephalogram, visual evoked cortical response, auditory evoked brainstem response, visual acuity and accomodation, color vision, visual fields, electroretinogram, extensive pulmonary function testing, and auditory-vestibular evaluation. Training in performance of the procedures that required active subject participation was accomplished concurrently with the medical evaluation. The entire process, which took about 20 hours per subject, was usually completed within the two weeks prior to exposure. Subject participation in the immediate pre-exposure, exposure, early post-exposure, and follow-up measurements usually required an additional 50 to 60 hours per man.

Overall Experiment Procedure. Subjects reported fasting to the laboratory at 0800 hours for the 2.0 ATA oxygen exposures. Initial preparation included placement of EEG and ECG electrodes and application of impedance tapes for cardiac output measurements. Vascular punctures for intravenous and intra-arterial catheters were then performed, and a thermistor probe was inserted into the rectum for deep body temperature measurement. An intravenous infusion of 5% dextrose in 0.225% sodium chloride solution was maintained throughout the exposure. Pre-exposure control measurements were performed at 1.0 ATA, followed by compression to 2.0 ATA, and the start of oxygen exposure for subject one. Oxygen exposure of the second subject was started 3 or 4 hours later. Measurements performed during exposure and post-exposure are summarized in Figs. 6 and 7. Each 2.0 ATA oxygen exposure of two subjects required nearly 36 hours for pre-exposure, exposure, and post-exposure procedures and measurements. Follow-up, rate of recovery measurements were obtained daily for the first post-exposure week and every other day for a second week.

Experiment procedures for the 1.5 ATA oxygen exposures were generally similar to those used for the 2.0 ATA series. Pre-exposure preparations for the 1.5 ATA series were started at 2000 hours (Fig. 8) to allow termination of the longer exposures at approximately the same time of day as the 2.0 ATA exposures. The overall experiment duration for two subjects at 1.5 ATA was nearly 48 hours.

Presentation of Results

This Progress Report summarizes the results of a preliminary analysis of an extremely large volume of data obtained in the 2.0 ATA and 1.5 ATA oxygen exposure series. Average data are

reported in most instances with presentation of individual data only when unique or especially noteworthy. Within each measurement category, data from both the 2.0 ATA and 1.5 ATA series are presented together to facilitate comparisons. Data from the previous 3.0 ATA series are included to indicate trends or contrasts.

BRAIN CORTICAL ELECTRICAL ACTIVITY

Electroencephalographic recording with the subject at rest and completely relaxed was accomplished during the measurement modules at the start and end of oxygen exposure at both pressures, with additional recording at regular intervals between modules during the longer exposures at 1.5 ATA (Figs. 6 and 8). Preliminary analysis of the records has revealed no significant abnormalities in any subject. As expected with the long exposure durations, EEG indications of intermittent drowsiness and sleep were observed in most subjects. Detailed analysis of the exposure records by the collaborating, experienced Neurologist-EEG Specialist is in progress.

EFFECTS ON VISUAL FUNCTION

Early and late oxygen exposure measurements of visual function were obtained in seven subjects at 2.0 ATA and in nine subjects at 1.5 ATA. Previous experience at 3.0 ATA indicated that loss of peripheral vision was a relatively sensitive index of oxygen effect on the eye and that the electroretinogram (ERG) was altered less consistently. Since ERG measurement required prior dark adaptation and pupillary dilation, which also affected other measurements, it was initially decided to measure ERG only in subjects who had visual field decrements. This decision was later reversed when ERG changes were found even in the absence of detectable reductions in visual field area.

Visual Acuity and Accommodation

There were no significant changes in either visual acuity or accommodation in any of the subjects exposed to oxygen at 2.0 ATA or at 1.5 ATA. Three subjects reported impaired or blurred vision during oxygen exposure at 2.0 ATA. Only one of the three had an associated decrement in peripheral vision. During oxygen exposure at 1.5 ATA, one subject reported mild impairment of vision that was not associated with any objective change in visual function.

Pupil Size

Only minor, inconsistent variations in pupil size were observed during oxygen exposure at either 2.0 or 1.5 ATA.

Visual Fields (Perimetry)

Measurements of relative visual field areas for right (OD) and left (OS) eyes in all seven subjects exposed to oxygen at 2.0 ATA are summarized in Table 3. Early exposure (0.3 hr) values in all subjects are similar to pre-exposure control values. Late exposure values obtained at an average duration of 8.3 hours are definitely decreased in subject S.A. and possibly decreased in subject C.H. who was coughing intermittently during the measurements. Relative visual field areas in S.A. (Fig. 9) decreased progressively during late exposure to 0.62 (OD) and 0.73 (OS) of the respective pre-exposure control values. Surprisingly, visual field measurements at 2.2 hours of recovery (breathing air at 1.0 ATA) showed no reversal of the decrement in peripheral vision. Even at 10.5 hours post-exposure, the visual field area of the left eye had apparently not fully returned to normal. This contrasted sharply with previous observations during the 3.0 ATA exposure series in which much larger visual field decrements reversed completely within 30 minutes after exposure termination (1984 Report).

Visual field measurements obtained during oxygen exposure at 1.5 ATA are summarized in Table 4. Peripheral vision was not detectably impaired at 0.6 and 15.0 hours of oxygen breathing in the nine subjects who completed the exposures with an average duration of 17.7 hours (Table 2).

Visual Evoked Cortical Response

The visual evoked cortical response (VER) like visual acuity, is primarily an index of central visual function. Relative amplitudes and latencies measured during oxygen exposure at 2.0 and 1.5 ATA are listed in Tables 5 and 6, respectively. Relative amplitudes of the VER were characteristically variable and did not consistently reveal any oxygen effects at either pressure. The more reliable VER latencies were remarkably stable during oxygen breathing at both 2.0 and 1.5 ATA. Average early and late exposure values at both pressures were nearly identical to pre-exposure control values, and even the individual values showed relatively little variability.

Electroretinography

Early exposure and post-exposure electroretinogram (ERG) measurements were obtained in four of the seven subjects exposed to oxygen at 2.0 ATA (Table 7). During the early post-exposure interval, all four subjects had decrements in ERG b-wave amplitude with little or no change in b-wave latency. Average values indicated a 50% decrease in amplitude about 1.4 hours after exposure termination.

Relative amplitude and latency of the ERG b-wave were tracked with repetitive measurements during and after oxygen exposure at 2.0 ATA in one subject (S.A.) (Fig. 10). Relative

TABLE 3.

VISUAL FIELDS DURING OXYGEN EXPOSURE AT 2.0 ATA

	Pre-Exposure		Early Exposure			Late Exposure		
	Control			Relative Field Size			Relative Field Size	
Subject	OD	OS	Duration (hr)	OD	OS	Duration (hr)	OD	OS
R.O.	1.00	1.00	0.20	1.05	1.09	8.37	0.96	1.07
J.S.	1.00	1.00	1.22	1.07	1.10	11.07	1.09	0.99
C.H.	1.00	1.00	0.28	0.99	0.96	7.22	0.86*	0.84*
P.F.	1.00	1.00	0.15	0.98	0.92	7.88	0.86	0.97
S.A.	1.00	1.00	0.10	0.97	0.93	7.40	0.87	0.86
R.C.	1.00	1.00	0.18	1.08	1.04	7.87	0.94	1.04
R.L.	1.00	1.00	0.15	0.99	0.93	8.25	1.11	1.10
Mean	1.00	1.00	0.33	1.02	1.00	8.29	0.96	0.98
SD	--	--	0.40	0.05	0.08	1.29	0.11	0.10

*Coughing during performance of measurements.

TABLE 4.

VISUAL FIELDS DURING OXYGEN EXPOSURE AT 1.5 ATA

	Pre-Exposure		Early Exposure			Late Exposure		
	Control			Relative Field Size			Relative Field Size	
Subject	OD	OS	Duration (hr)	OD	OS	Duration (hr)	OD	OS
C.C.*	1.00	1.00	0.70	1.04	1.12	2.73	--	1.06
B.K.	1.00	1.00	0.60	0.94	1.02	14.25	0.98	1.02
G.L.	1.00	1.00	0.40	0.97	0.97	16.63	1.11	1.01
M.M.	1.00	1.00	0.48	1.17	1.03	14.33	1.22	1.17
C.S.	1.00	1.00	0.62	1.10	1.10	16.40	1.05	1.07
J.U.	1.00	1.00	0.42	1.03	0.94	14.40	1.05	0.96
J.M.	1.00	1.00	0.58	0.96	0.99	14.72	0.94	0.95
D.H.	1.00	1.00	0.73	0.99	0.99	14.55	1.12	0.99
S.J.	1.00	1.00	0.55	0.97	1.05	14.57	1.02	1.05
J.G.	1.00	1.00	0.65	1.07	1.04	15.10	1.06	1.02
N-10								
Mean	1.00	1.00	0.57	1.02	1.03	13.77	1.06	1.03
SD	--	--	0.11	0.07	0.06	3.97	0.08	0.06
N-9 (w/o C.C.)								
Mean	1.00	1.00	0.56	1.02	1.01	15.00	1.06	1.03
SD	--	--	0.11	0.08	0.05	0.90	0.08	0.07

* Subject requested termination of exposure at 3.0 hours.

FIGURE 9.

VISUAL FIELD AREAS IN ONE SUBJECT (S.A.) BEFORE, DURING, AND AFTER OXYGEN EXPOSURE AT 2.0 ATA FOR 10.5 HOURS

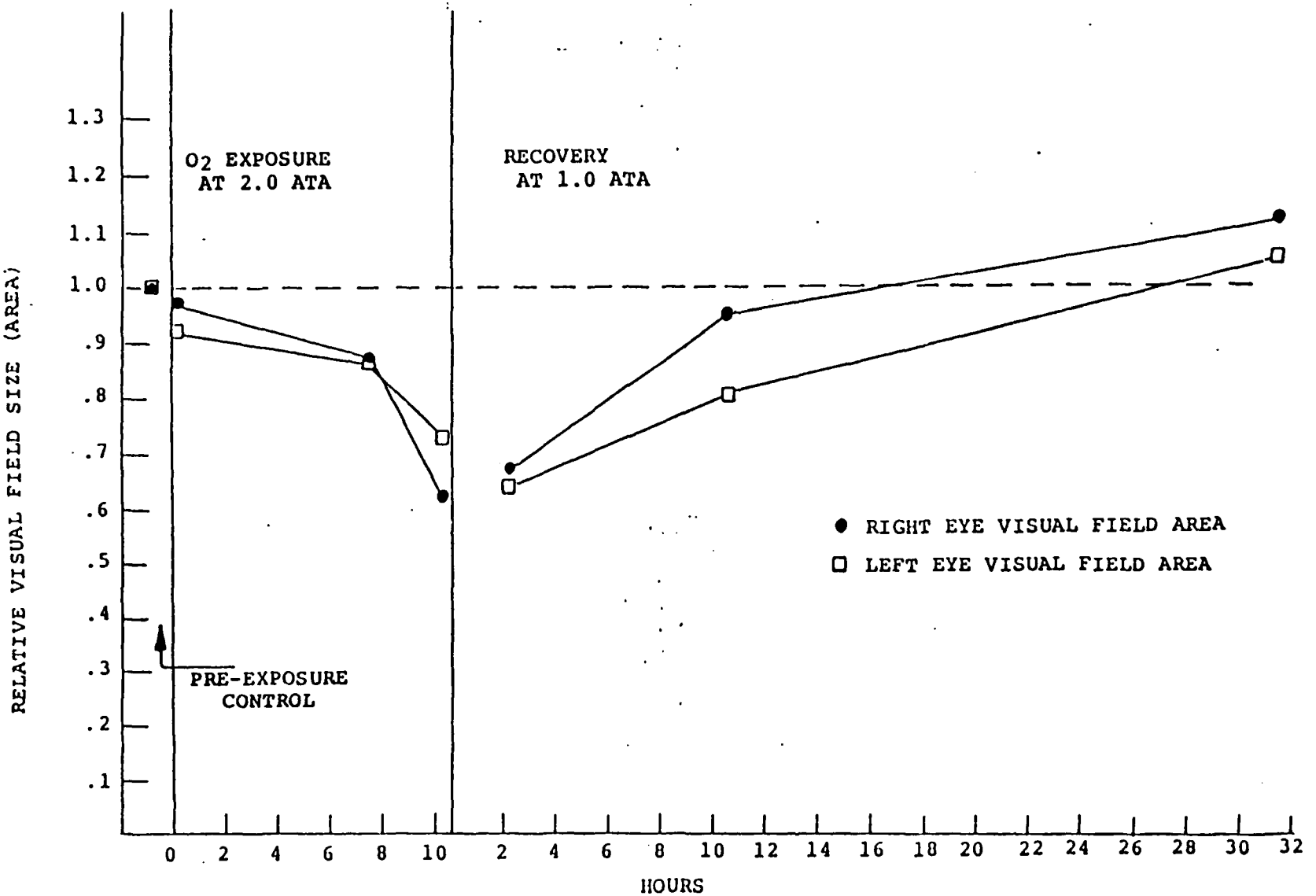


TABLE 5.

RELATIVE AMPLITUDE AND LATENCY
OF VISUAL EVOKED CORTICAL RESPONSE
DURING OXYGEN EXPOSURE AT 2.0 ATA

	Pre-Exposure		Early Exposure			Late Exposure		
	Control		Duration	Relative		Duration	Relative	
Subject	Amplitude	Latency	(hr)	Amp.	Lat.	(hr)	Amp.	Lat.
R.O.	1.00	1.00	0.60	1.42	1.06	8.80	1.07	1.07
J.S.	1.00	1.00	1.67	1.35	1.00	9.68	1.45	0.95
C.H.	1.00	1.00	0.67	0.98	1.00	7.53	1.06	1.00
P.F.	1.00	1.00	0.75	1.97	0.93	--	--	--
S.A.	1.00	1.00	0.45	1.48	1.01	8.68	1.44	1.02
R.C.	1.00	1.00	0.68	2.22	0.91	8.18	1.55	0.91
R.L.	1.00	1.00	0.53	0.71	0.97	8.80	1.27	1.02
N-7								
Mean	1.00	1.00	0.77	1.45	0.98	--	--	--
SD	--	--	0.41	0.52	0.05	--	--	--
N-6 (w/o P.F.)								
Mean	1.00	1.00	0.77	1.36	0.99	8.61	1.31	1.00
SD	--	--	0.45	0.51	0.05	0.72	0.21	0.06

TABLE 6.

RELATIVE AMPLITUDE AND LATENCY
OF VISUAL EVOKED CORTICAL REPONSE
DURING OXYGEN EXPOSURE AT 1.5 ATA

	Pre-Exposure		Early Exposure			Late Exposure		
	Control		Duration	Relative		Duration	Relative	
Subject	Amplitude	Latency	(hr)	Amp.	Lat.	(hr)	Amp.	Lat.
C.C.	1.00	1.00	1.07	1.29	0.98	--	--	--
B.K.	1.00	1.00	1.03	0.95	0.98	14.55	0.75	0.98
G.L.	1.00	1.00	0.67	0.43	1.03	16.92	0.83	1.01
M.M.	1.00	1.00	0.97	2.00	0.98	14.60	2.25	0.92
C.S.	1.00	1.00	0.95	1.17	0.98	14.87	0.94	0.95
J.U.	1.00	1.00	0.70	1.06	1.03	14.67	1.05	1.00
J.M.	1.00	1.00	1.00	1.19	0.99	14.97	1.34	0.97
D.H.	1.00	1.00	1.07	0.75	1.10	14.88	1.25	1.03
S.J.	1.00	1.00	0.92	1.22	0.89	14.95	1.74	1.06
J.G.	1.00	1.00	1.02	1.18	0.99	14.70	0.87	0.98
N-10								
Mean	1.00	1.00	0.94	1.12	1.00	--	--	--
SD	--	--	0.14	0.40	0.05	--	--	--
N-9 (w/o C.C.)								
Mean	1.00	1.00	0.92	1.11	1.00	15.01	1.22	0.99
SD	--	--	0.14	0.42	0.06	0.73	0.49	0.04

TABLE 7.

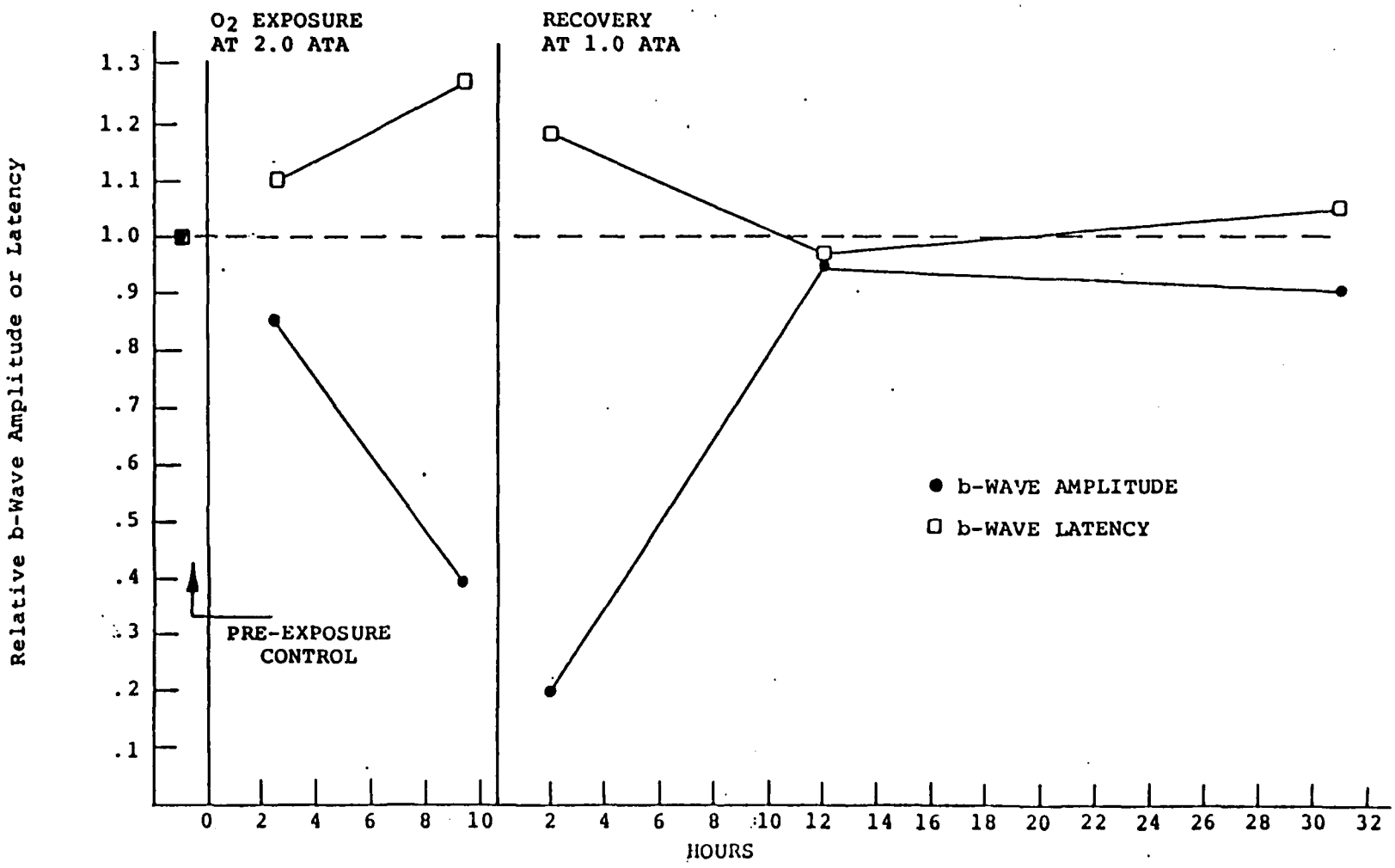
RELATIVE AMPLITUDE AND LATENCY OF ERG B-WAVE
BEFORE, DURING, AND AFTER OXYGEN EXPOSURE AT 2.0 ATA

Subject	Stimulus*	Control Amplitude	Control Latency	Exposure Duration (hr)	Early Exposure Relative Amplitude	Early Exposure Relative Latency	Post-Exposure Interval (hr)	Post-Exposure Relative Amplitude	Post-Exposure Relative Latency
C.H.									
	4B	1.00	1.00	2.53	.82	1.06	0.80	.75	1.04
	8B	1.00	1.00		.47	1.15		.77	1.03
	16B	1.00	1.00		.71	1.03		.71	1.07
	16R	1.00	1.00		.62	1.09		.58	1.07
S.A.	4B	1.00	1.00	2.45	.96	1.08	2.00	.30	1.08
	8B	1.00	1.00		.85	1.10		.20	1.18
	16B	1.00	1.00		.94	1.21		.17	1.06
	16R	1.00	1.00		.96	1.09		.79	0.85
R.C.									
	4B	1.00	1.00	1.73	.74	.94	1.03	.33	.90
	8B	1.00	1.00		.81	.95		.51	.86
	16B	1.00	1.00		.64	.97		.50	.90
	16R	1.00	1.00		.68	.98		.46	.86
R.L.									
	4B	1.00	1.00	1.90	1.09	.99	1.63	.57	1.15
	8B	1.00	1.00		.88	.85		.44	.88
	16B	1.00	1.00		1.15	.99		.57	.98
	16R	1.00	1.00		1.19	1.01		.47	1.06
Mean±S.D.	4B			2.15±0.40	0.90±0.15	1.02±0.06	1.37±0.55	0.49±0.21	1.04±0.11
	8B				0.75±0.19	1.01±0.14		0.48±0.23	0.99±0.15
	16B				0.86±0.23	1.05±0.11		0.49±0.23	1.00±0.08
	16R				0.86±0.26	1.04±0.06		0.58±0.15	0.96±0.12

*STIMULUS CONDITIONS
4B - Low intensity blue light flash
8B - Medium intensity blue light flash
16B - High intensity blue light flash
16R - High intensity red light flash

FIGURE 10.

AMPLITUDE AND LATENCY OF ERG B-WAVE IN ONE SUBJECT (S.A.)
BEFORE, DURING, AND AFTER OXYGEN EXPOSURE AT 2.0 ATA FOR 10.5 HOURS

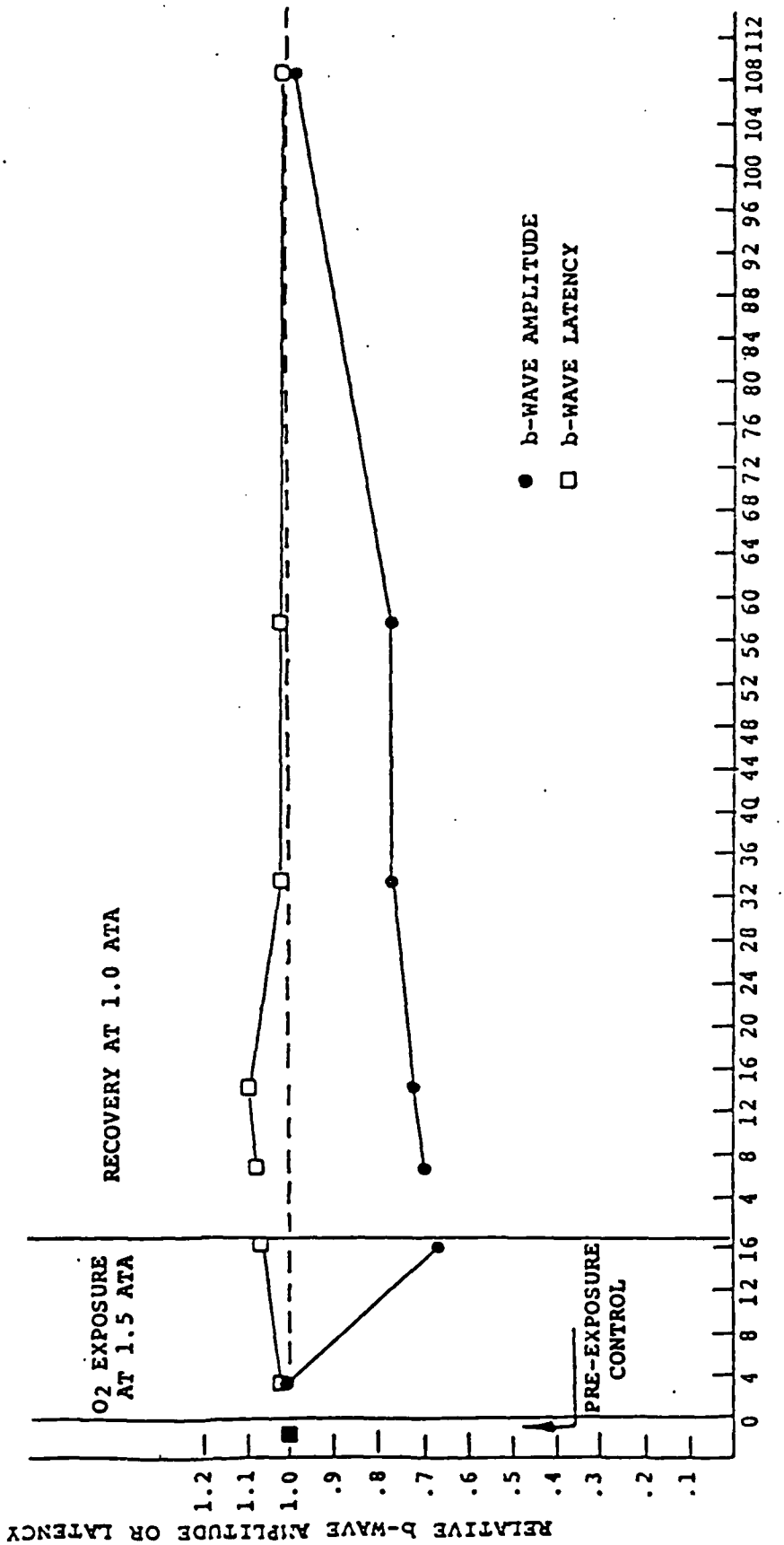


amplitude of the b-wave response to a medium intensity blue light flash (8B) decreased from 0.85 of the pre-exposure control value at 2.4 hours of exposure to 0.39 at 9.4 hours, and further decreased to 0.20 at 2.0 hours post-exposure. The decrease in amplitude was associated with a smaller increment in relative latency. Both amplitude and latency had returned to pre-exposure control values by 12.0 hours post-exposure. Recovery of ERG b-wave amplitude was also documented in subjects R.C. and R.L., respectively, at 12.4 and 15.8 hours post-exposure.

Both early and late exposure ERG measurements were obtained in all nine subjects who completed oxygen exposures at 1.5 ATA. Average values at 2.6 and 16.6 hours of exposure indicated that neither amplitude nor latency of the b-wave were altered from pre-exposure control values. However, individual data show that subject B.K. had a decrease in ERG b-wave amplitude to 0.67 of the control value at 16.0 hours of exposure (Fig. 11). These individual data are also unique in that b-wave amplitude had not returned to the pre-exposure control value at 2.4 days post-exposure. The next measurement at 4.5 days indicated complete ERG recovery. Decrements in ERG b-wave amplitude caused by oxygen exposure at 2.0 ATA (Table 7), as well as those that occurred during the 3.0 ATA oxygen exposure series, were all fully reversed by 12 to 24 hours after exposure termination.

FIGURE 11.

AMPLITUDE AND LATENCY OF ERG B-WAVE IN ONE SUBJECT (B.K.)
BEFORE, DURING, AND AFTER OXYGEN EXPOSURE AT 1.5 ATA FOR 17.0 HOURS



AUDITORY-VESTIBULAR FUNCTIONS

The initial Phase of Predictive Study V utilized routine audiologic testing to assess effects on the auditory system. In contrast, the 2.0 and 1.5 ATA Phases of PS V utilized new techniques that were considered to be sensitive to subtle alterations in auditory system integrity. Consequently, in addition to routine puretone air and bone conduction audiometry for frequencies 250-8000 Hz, monosyllabic word recognition studies at normal and high sound pressure levels, and complete acoustic immitance studies including tympanometry, crossed and uncrossed acoustic reflex thresholds and reflex decay testing, the following pre-exposure and post-exposure measurements were performed under controlled laboratory conditions at the Speech and Hearing Center of the Hospital of the University of Pennsylvania:

1. A complete battery of auditory evoked potentials including; a) auditory brainstem responses at both slow and rapid repetition rates (11.1/sec and 71.1/sec) in an effort to show the effect of stressing the auditory system; b) middle latency components of the auditory evoked potential; c) late auditory evoked responses; d) puretone threshold at ultra-audiometric frequencies (10,000-20,000 Hz; e) Masking Level Differences (MLD) used to assess binaural processing in the auditory brainstem; and f) electronystagmography.

Results of Controlled Laboratory Tests. A preliminary analysis of results of the aforegoing test battery for both pre- and post-exposure conditions showed minimal abnormality on both conventional and ultra-high frequency puretone measures, acoustic immittance measures and auditory evoked potentials. However, four subjects of the 2.0 ATA and 1.5 ATA Phases presented with an abnormal reduced vestibular response primarily on the left side during post-exposure ENG assessment, suggesting the possibility of an effect on the peripheral vestibular apparatus.

Observations During Exposure to Hyperoxia. In addition to the aforementioned auditory assessment performed under controlled laboratory conditions at the Speech and Hearing Center, a series of auditory tests were performed during the exposure period on most subjects. These included; 1) ultra-high frequency puretone testing at octave frequencies 10,000-16,000 Hz and 20,000 Hz; 2) tympanometry and a 1000 Hz (105 dB) uncrossed acoustic reflex screen; 3) auditory brainstem responses to a minimal number of averages (1000) for five subjects.

Preliminary analysis of data from ultra-high frequency audiometry for early and late modules at 1.5 ATA indicated threshold values above 10,000 Hz that fell well outside of the one standard deviation range of normal control subjects reported by Fausti et al. Similar findings apply for the 2.0 ATA condition. The most noticable change from normal occurred at 16,000 Hz. Tympanometry showed the majority of middle ear systems to be normal and intact during the hyperoxic exposures. Exceptions

included a few minor cases of negative pressure tympanograms indicating Eustachian tube dysfunction, one case of a positive pressure tympanogram, and some selected examples of deep tympanograms assumedly due to flaccid tympanic membrane.

Auditory brainstem responses were recorded in five subjects during the 1.5 ATA exposure. The waveform morphology for these five subjects was quite clear and absolute latencies for primary peaks I-III-V as well as inter-peak latencies I-III, I-V, III-V were all within normal limits during the exposure period. These results sugges two things: a) measurement of short-latency auditory evoked potentials (auditory brainstem responses) is technologically feasible in the chamber and b) exposure to O_2 at 1.5 ATA does not seem to have an adverse effect on auditory brainstem transmission.

Application of Methods to 2.5 ATA Exposure Phase. The methods employed in the 2.0 and 1.5 ATA Phases will be applied as well to the exposures at 2.5 ATA.

MENTAL AND PSYCHOMOTOR FUNCTION

In normal subjects breathing oxygen at rest, convulsions are rare at 2.0 ATA. Nevertheless, oxygen may have subtle effects on mental and psychomotor function during extremely prolonged exposures at 2.0 and 1.5 ATA. Detection of such effects is complicated by the possibility that influences of subject fatigue and/or boredom will be superimposed to some degree on any effects of hyperoxia.

The series of tests used to evaluate mental and psychomotor function at 2.0 and 1.5 ATA are identical to those used previously at 3.0 ATA. Specific tests used and the times required for their performance are the following: a visual digit span test of short term memory ability (120 seconds), a key insertion test of finger dexterity ability (60 seconds), an operations test of number facility and general reasoning abilities (120 seconds), and a visual reaction time test of response speed ability (20 trials). The entire battery was administered one or more days before exposure, during early and late exposure, and one or more days after exposure termination.

Appendix 2 contains a summary of results obtained at 2.0 ATA (Appendix Table 1 and Figs. 1 to 4) and at 1.5 ATA (Appendix Table 2 and Figs. 5 to 8). Early and late exposure measurements were obtained at average times of 0.8 and 8.5 hours at 2.0 ATA and 1.0 and 14.8 hours at 1.5 ATA. For most of the measured parameters, average test scores remained remarkably stable during oxygen exposure. Although the 1.5 ATA exposures were nearly twice as long as those at 2.0 ATA, the measurement schedule was less condensed and allowed the subjects more time for rest. More detailed analysis will be required to evaluate subtle trends and individual changes. Identification of possible oxygen effects among superimposed influences of subject fatigue and boredom will

be aided by data from 20-hour control exposures (air at 1.0 ATA) that are scheduled to be performed later this year in subjects who were studied at 2.0 and 1.5 ATA.

RESPIRATORY FUNCTIONS, GAS EXCHANGE, AND BODY TEMPERATURE

This section incorporates a number of measurements related principally to resting respiratory functions and spontaneous ventilation. Purposes include (1) monitoring of the subject's general respiratory status during oxygen exposures, (2) investigation of ventilatory parameters as potential indicators of oxygen effect on the integrated neural and neuro-chemical mechanisms of respiratory control (3.0 ATA and 2.0 ATA series), and (3) investigation of ventilatory parameters as potential indicators of hyperoxic effects on the neuro-mechanical functions of the airways, lungs and the respiratory muscles (2.0 ATA and 1.5 ATA series). The measurements reported below include:

1. Resting ventilatory parameters and ventilatory responses to progressive hypoxia and progressive hypercapnia.
2. Gas exchange and respiratory exchange ratio.
3. Peak forces generatable by respiratory muscles and a skeletal muscle group.
4. Body temperature.

As this Progress Report is written, data processing and reduction of the 2.0 and 1.5 ATA exposures has been underway for only a short time and the information currently available is not complete.

1. Resting Ventilatory Parameters and Ventilatory Responses to Hypoxia and Hypercapnia.

Results of the 3.0 ATA exposure series have been reported in a brief communication (25). Important findings (summarized in Figs. 12a and 12b) were reported in part in the 1984 Progress Report. They include identification of potential physiologic, toxic and combined physiologic/toxic effects of hyperoxia on respiratory control functions in twelve subjects who did not convulse (summarized in Fig. 12a). A working definition of toxic as contrasted to physiologic effects of hyperoxia is given in Fig. 13. A summary of the findings in the single subject who did experience a convulsion is given in Fig. 12b. It is important that the changes indicated began well before the convulsion onset, were progressive, and were accelerating to onset of convulsion, in the absence of preconvulsive changes in the electroencephalogram. These findings are important to experimental design of the exposures at 2.5 ATA O_2 in the coming year, both for subject safety and purposes of investigation.

Detailed results for the 2.0 ATA and the 1.5 ATA exposure series are not currently available. Data available for processing and analysis are the same as those for the 3.0 ATA series. Data reduction has begun, and selected observations are cited below.

Periodic Breathing (Observation). Visual observation while monitoring strip chart recordings during the exposures and

FIGURE 12a.

SUMMARY OF CHANGES IN RESPIRATORY PARAMETERS
IN GROUP OF 12 SUBJECTS WHO DID NOT CONVULSE
(3.0 ATA O_2 x 3.5 hr. exposure)

1. PHYSIOLOGIC INCREASE IN VENTILATION.
2. PHYSIOLOGIC INCREASE IN TIDAL VOLUME.
3. ASSOCIATED DECREASE IN END-TIDAL PCO_2.
4. NO EFFECT ON EXPIRATORY TIME.
5. TOXIC EFFECT ON RESPIRATORY FREQUENCY.
6. DUAL EFFECTS ON INSPIRATORY TIME.

FIGURE 12b.

SUMMARY OF CHANGES IN RESPIRATORY PARAMETERS
OF SINGLE SUBJECT WHO CONVULSED
(3.0 ATA O_2, convulsion at 3.0-hr. exposure)

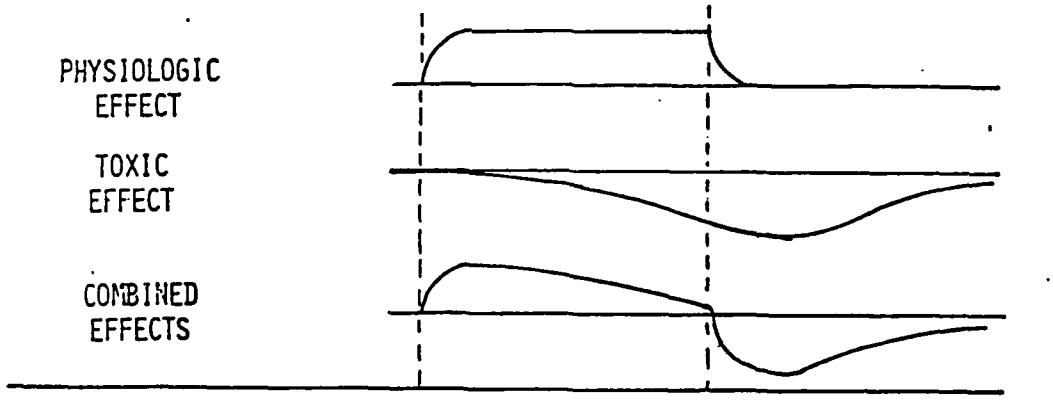
STARTING ABOUT 40 MIN. BEFORE CONVULSION, THE FOLLOWING DELAYED-ONSET, RAPIDLY PROGRESSIVE CHANGES OCCURRED:

1.	INCREASE IN EXPIRATORY TIME	(2 SEC TO 7 SEC)
2.	RECIPROCAL DECREASE IN RESP. FREQUENCY	(18 BR/MIN TO 7 BR/MIN)
3.	REDUCTION IN PULMONARY VENTILATION	(14 ℓ/MIN TO 6.5 ℓ/MIN)
4.	INCREASE IN END-TIDAL PCO_2	(33 MMHG TO 43 MMHG)

FIGURE 13.

WORKING DEFINITIONS OF PHYSIOLOGIC
AND TOXIC EFFECTS OF HYPEROXIA

	Physiologic	Toxic
Onset at start of Hyperoxia	Rapid	Gradual
Change During Exposure	None	Progressive
Recovery at End of Exposure	Rapid	Delayed



Temporal pattern of change for combined effects is the algebraic summation of separate physiologic and toxic effects. Its time course of change can be expected to be more complex than either of its constituent components.

closer examination subsequently has revealed episodes of periodic breathing, particularly for some of the subjects in the prolonged exposures of the 1.5 ATA series (Fig. 14). This type of periodic breathing is not related to the preconvulsive changes in respiratory pattern and timing observed in the subject of the 3.0 ATA series who convulsed (Figs. 15 and 16). Rather, it resembles in form, but not in origin or degree or significance, the oscillatory respiratory pattern of the Cheyne-Stokes type, which can result from combinations of extended circulation time between the pulmonary vascular bed to peripheral and central respiratory chemoreceptors, and extremes of respiratory CO_2 reactivity.

A possible explanation for the genesis of episodic respiratory oscillations in the current investigations involves (1) effects of hyperoxia on ventilation, (2) effects of hyperoxia on ventilatory control, and (3) drowsiness or sleep. Hyperoxia depresses the slope of the ventilatory response to hypercapnia (4) while at the same time ventilation during CO_2-free breathing increases, with resultant arterial hypocapnia (4, 10, Fig. 17). The resultant reduction in brain perfusion rate and increase in circulation time, with reduced respiratory reactivity to CO_2 (4) may together not be sufficient to produce the periodic respiration, which was not observed during the 3.5 hour exposures at 3.0 ATA. However, during the longer exposures at 1.5 ATA it was inevitable that the subjects became sleepy, and there was time (when they were not actively engaged in measurements) for them to manifest drowsiness and sleep. The periodic respiration shown in Fig. 14 occurred during such a period; drowsiness and sleep by themselves reduce respiratory CO_2 reactivity; the combination of drowsiness or sleep with the effects of hyperoxia cited may therefore be a sufficient condition for genesis of periodic respiration in some individuals.

This is also important to the design and performance of the 2.5 ATA exposure series, since arterial PCO_2 must become elevated during extended non-breathing periods. In the absence of ventilation, end-tidal PCO_2 levels cannot be measured. While this was of little consequence with respect to the very small potential for CNS convulsions during the 1.5 ATA series, it will be extremely critical in the planned 2.5 ATA series. Measures must therefore be taken to keep the Subjects awake, and to monitor for periodic respiration during those experiments. This is in addition to watching for the preconvulsive respiratory manifestations observed in the single subject of the 3.0 ATA series, which apparently resulted from a respiratory control system expression of central nervous system oxygen toxicity.

Ventilatory Responses to Progressive Hypoxia and Hypercapnia. In addition to measurements described above, we determined ventilatory responses to progressive hypoxia and to progressive hypercapnia both before and within several hours after the 1.5 ATA hyperoxic exposures were completed. These were made to determine for normal men if the longest exposures to continuous hyperoxia of the current series would affect either

FIGURE 14.

EPISODE OF RESPIRATORY OSCILLATION. SUBJECT AT 1.5 ATA, ABOUT 8 HR. 45 MIN. OF O_2 EXPOSURE.
TOP PANEL: END OF 5-MIN. PERIOD OF EEG MEASUREMENT (SUBJECT SUPINE-AWAKE).
BOTTOM PANEL: POST EEG MEASUREMENT (SUBJECT SUPINE - NO EXPERIMENT ACTIVITY).

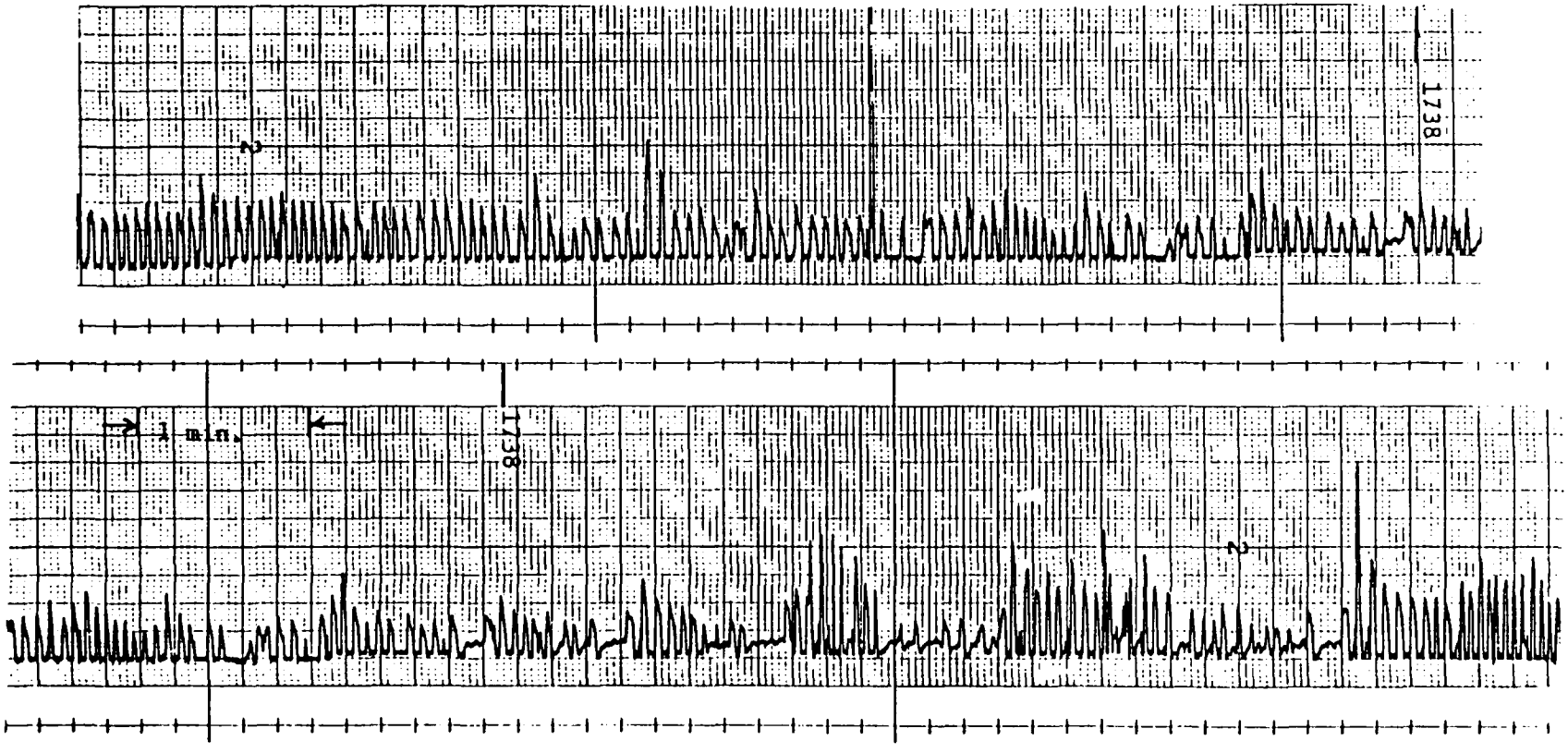


FIGURE 15.

CHANGES IN PATTERN OF BREATHING AND IN INSPIRATORY FLOW WAVEFORMS PRIOR TO, AT ONSET OF, AND FOLLOWING RECOVERY FROM HYPEROXIC CONVULSION

(3.0 ATA exposure phase)

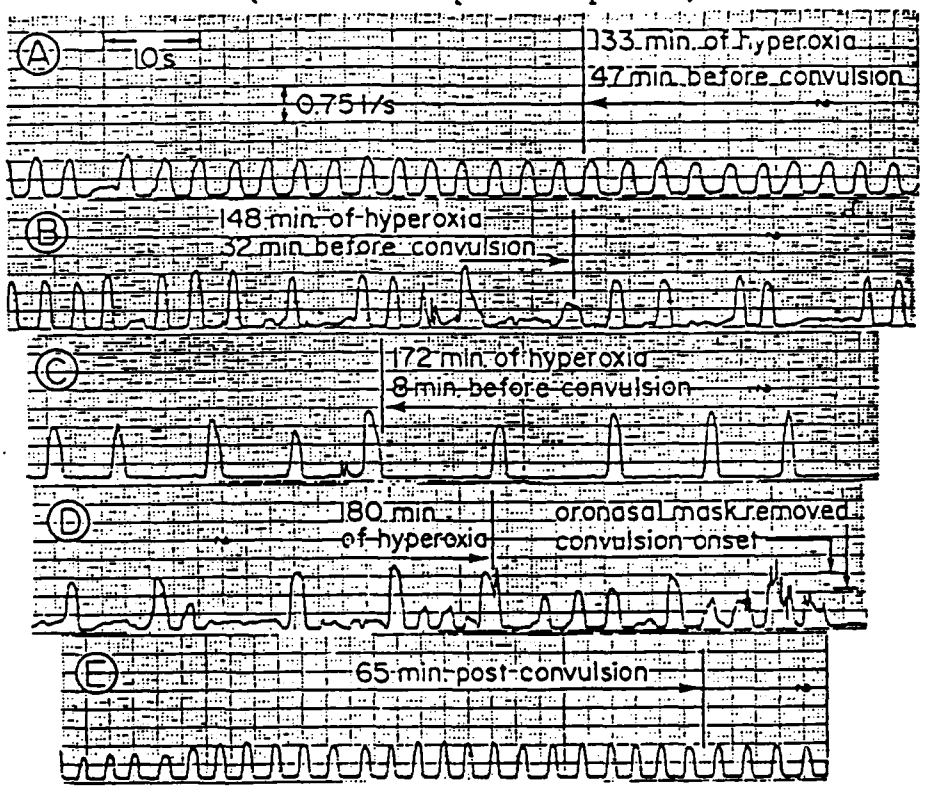


FIGURE 16.

EFFECTS OF O_2 AT 3ATA FOR 3.5 HOURS ON T_I, T_E AND F.
COMPARISON OF CHANGES IN ONE SUBJECT WHO CONVULSED
WITH THOSE OF GROUP (N = 12) WITHOUT CONVULSION

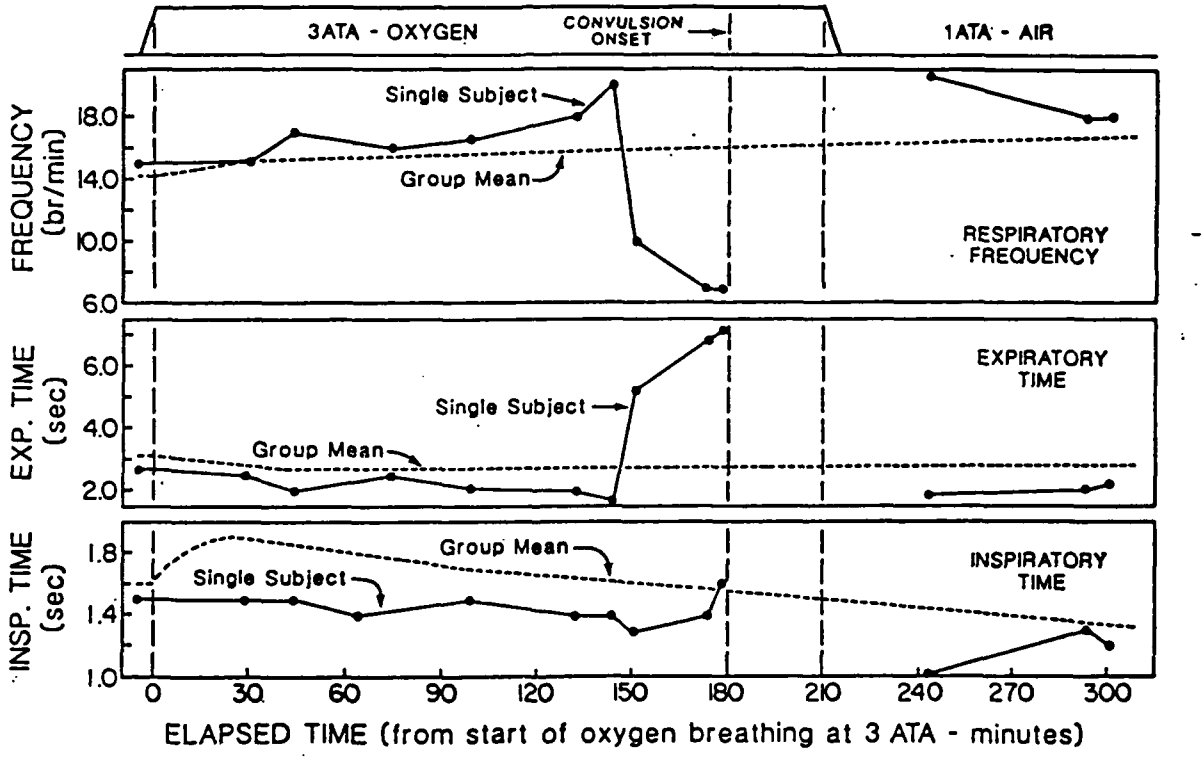
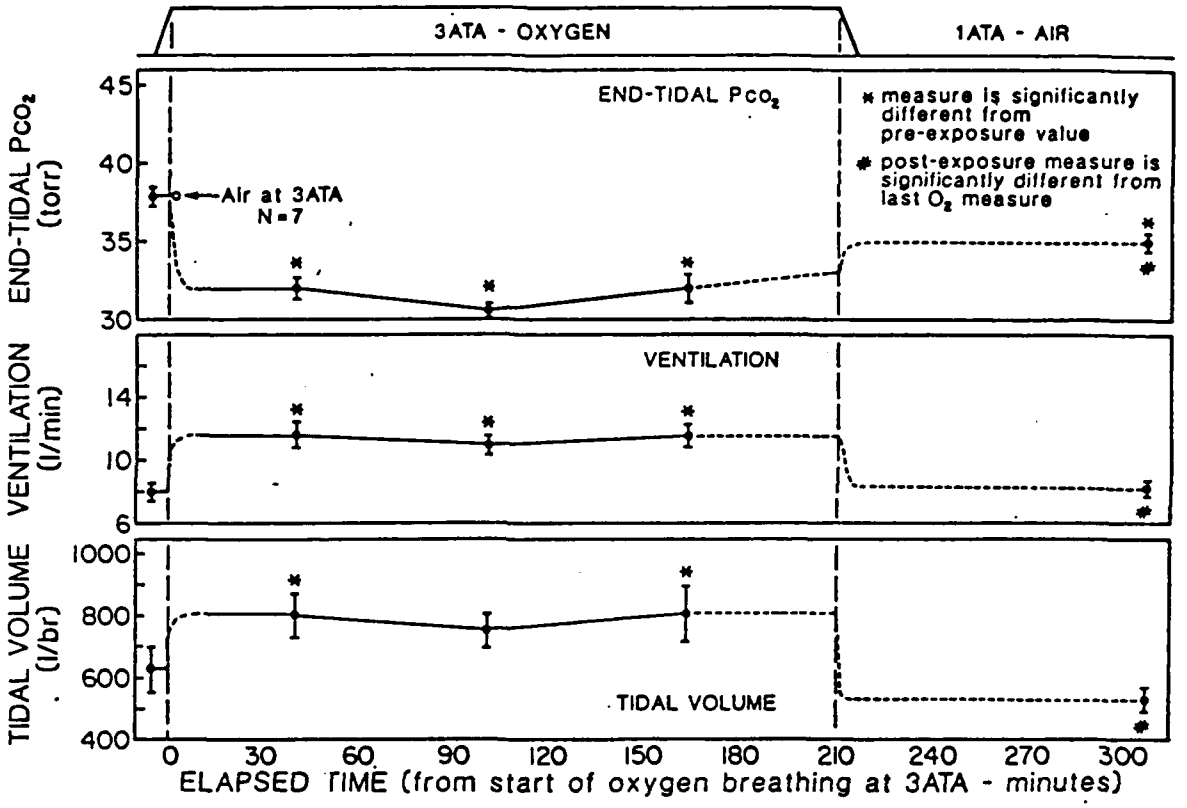


FIGURE 17.

EFFECTS OF O_2 AT 3ATA FOR 3.5 HOURS ON V_T, $\dot{V}$ AND $P_{ET}CO_2$
(mean ± SEM, N = 12)



the functioning of the peripheral (carotid and aortic body) respiratory chemoreceptors or of the central respiratory receptors.

Analyses for only a single subject are available at this time. The ventilatory response to hypoxia was essentially the same after the approximately 18-hour exposure to oxygen at 1.5 ATA as it was before, and the slope of the ventilatory response to CO_2 was not altered, although the post-exposure curve was shifted to the left relative to pre-exposure curve. These measurements were made in the period 30 to 90 minutes following termination of hyperoxia. These preliminary findings for a single subject in our 1.5 ATA series are in contrast to a brief report for patients exposed to 2.4 ATA oxygen, 90 min./day on alternate days for periods to 90 days (26). It was stated there that the slope of the respiratory response to CO_2 (measured during the "treatment") was flattened and shifted to the right and that the (peripheral) chemoreceptor response to CO_2 after oxygen exposure was reduced. In another project in this Institute on the effect of 62-67 hour exposures of cats to 100% O_2 at 1 ATA (27), it was observed that various degrees of blunting occurred, both of ventilatory and carotid chemoreceptor responses to hypoxia. The extensive data we have accumulated will be analyzed with these findings in mind, and the results will be incorporated into planning of the 2.5 ATA series.

2. Gas Exchange and Respiratory Exchange Ratio

Gas exchange has been measured in each of the three exposure series (3.0 ATA, 2.0 ATA, 1.5 ATA) for evaluation of extreme hyperoxia on metabolic state. Also, previous reports concerning hyperoxic gas mixtures used at 1 ATA to study regulatory mechanisms of exercise have shown increased O_2 uptake ($\dot{V}O_2$), reduced CO_2 elimination rate ($\dot{V}CO_2$), and reduced respiratory exchange ratio (R) (28). The rationale for these observations has been a shift toward increased body fat metabolism during even low level hyperoxia (28). Recently, the accuracy of gas exchange measurements during hyperoxia has been questioned on technical and procedural grounds (29).

The results described here apply only to pre-exposure and post-exposure measurements. As shown in Table 8, mean values of R were less than control values following oxygen exposure for the 2.0 ATA series (rest measurements only), and for the 1.5 ATA series (both rest and exercise measurements). The pre- and post-exposure values of R were unaffected by the 3 ATA exposures and by the 2.0 ATA exposures (exercise). There was no consistency in pre-exposure vs post-exposure changes in VCO_2 and VO_2 as causative factors in the changed values of R.

The changes in gas exchange parameters described above are small, and represent residual changes following termination of oxygen exposure. Of greater potential significance are similar measurements obtained during the hyperoxic exposures.

TABLE 8.

GAS EXCHANGE PARAMETERS MEASURED BEFORE AND AFTER CONTINUOUS OXYGEN EXPOSURES AT 3.0, 2.0 and 1.5 ATA
(mean values)

	3.0 ATA Series			2.0 ATA Series			1.5 ATA Series		
	$\dot{V}CO_2$	$\dot{V}O_2$	R	$\dot{V}CO_2$	$\dot{V}O_2$	R	$\dot{V}CO_2$	$\dot{V}O_2$	R
MEASUREMENTS AT REST									
	(n=13)			(n=7)			(n=9)		
Pre-Exposure	211	226	0.93	214	234	0.92	191	233	0.82
Post-Exposure	219	244	0.90	189	240	0.79	191	265	0.72
MEASUREMENTS DURING EXERCISE									
				(n=7)			(n=8)		
Pre-Exposure	-	-	-	1,242	1,330	0.93	1,350	1,495	0.91
Post-Exposure	-	-	-	1,216	1,315	0.92	1,274	1,568	0.83
Time Post-Exposure	04:56			02:10			02:20		

$\dot{V}CO_2$ and $\dot{V}O_2$ in ml/min STPD
Time post-exposure (hr:min) - elapsed time following end of oxygen exposure

However, the accuracy of gas exchange measurements during hyperoxia can be compromised by a number of potential technical and procedural difficulties (29). Improvements in measurement procedure were incorporated into the 2.0 ATA and 1.5 ATA series and it is anticipated that analysis of these results will provide valid measures of gas exchange during those hyperoxic exposures.

3. Body Temperature

Poisoning of the central nervous system has been associated with fall in body temperature in rats not related to decrease in metabolic rate or to pressure/density effects on heat loss, but presumably due to poisoning by O_2 of CNS structures associated with control of body temperature (20). Observation of rectal temperatures in the 3.0 ATA series revealed that body temperature of the single subject who convulsed decreased at an accelerating rate in the period prior to onset of the convulsion (Fig. 18). Body temperature for the group of subjects who did not convulse also appeared to begin decreasing at an accelerating rate toward the end of the full 3.5-hour exposure period (Fig. 18). This finding is of extreme importance to the planned 2.5 ATA exposure series as a potential preconvulsive index of CNS oxygen poisoning.

Body temperatures were continuously monitored in both the 2.0 ATA and 1.5 ATA series of oxygen exposures. Although the data have not yet been quantitatively processed for analysis, it is apparent by visual inspection that the results at 2.0 ATA may resemble those for the 3.0 ATA group who did not convulse (Fig. 18). Thus, for the 2.0 ATA series, it appears that an initial small increment after compression is followed by a decline, while for the 1.5 ATA series, this pattern appears to be absent.

4. Muscle Strength (Respiratory Muscles; Skeletal Muscle)

The potential for modification of muscle function by neural or direct muscle effects of hyperoxia was appraised by two separate measures of muscle strength. One measured maximal sustainable airway pressures generated by the respiratory muscles against the blocked airway. The other measured the maximal force generated by the forearm muscles concerned with handgrip, and the endurance of this muscle group at 80% of maximum handgrip force.

Maximal airway pressures were measured at both extremes of lung volume (inspiratory pressure with empty lung, expiratory pressure with full lung) and at FRC (Table 9). As reported previously, there were no appreciable changes associated with hyperoxia during the 3.0 ATA series. Greater changes were observed, of the order of 9% to 26%, in the 2.0 ATA and 1.5 ATA oxygen exposure series (late O_2 exposure compared to air control or early O_2 exposure). However, changes are not consistent across the 2.0 ATA and 1.5 ATA series. Thus, at 2.0 ATA, mean values of inspiratory pressure decreased, while expiratory

FIGURE 18.

EFFECTS OF O_2 AT 3ATA ON BODY TEMPERATURE.
COMPARISON OF CHANGES IN ONE SUBJECT WHO CONVULSED
WITH THOSE OF GROUP (N=12) WITHOUT CONVULSION

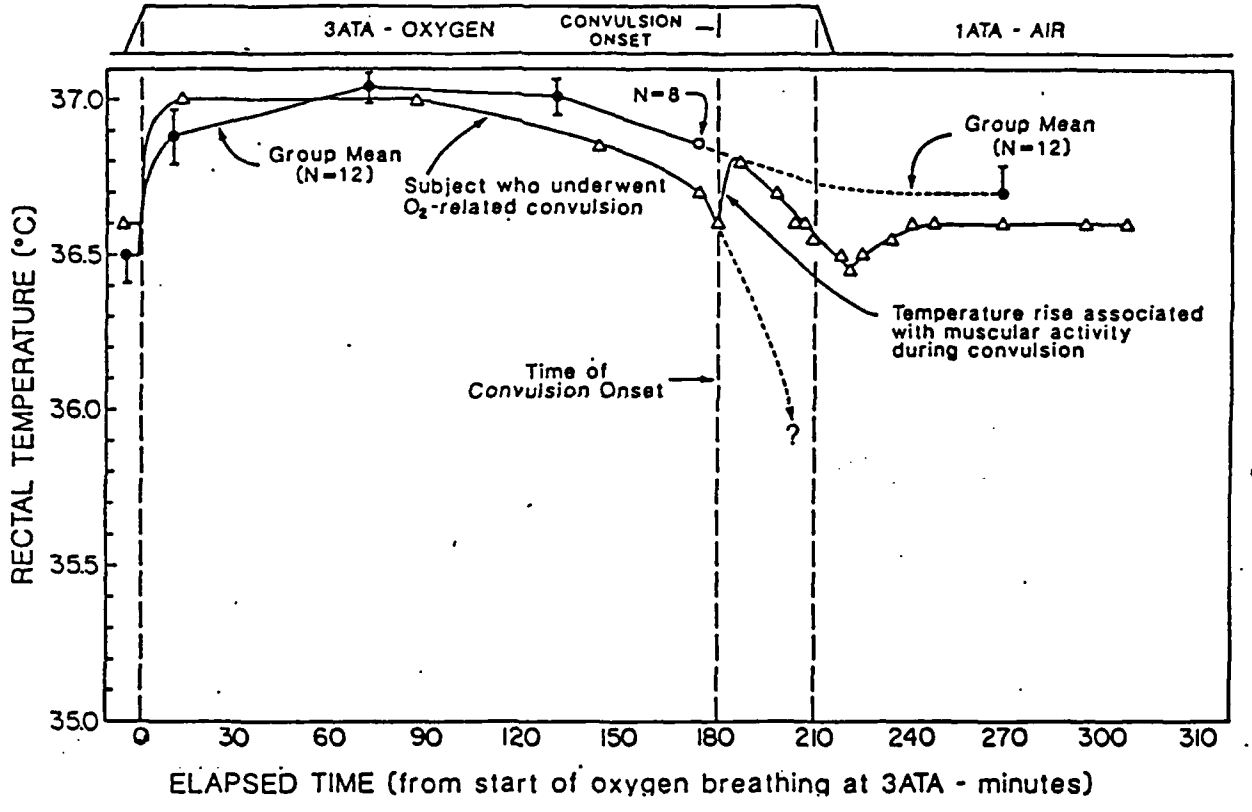


TABLE 9.

MAXIMAL PRESSURES GENERATED BY LUNGS AGAINST BLOCKED AIRWAY

INSPIRATORY PRESSURES WITH EMPTY LUNGS AND AT FRC
EXPIRATORY PRESSURES WITH FULL LUNGS AND AT FRC

(Mean Values)

MEASUREMENT	INSPIRATORY		EXPIRATORY	
	(Empty lung)	(FRC)	(Full lung)	(FRC)
		2.0 ATA Series (n-4)		
Control (1 ATA air)	137	125	116	116
Exposure (final O_2 module)	101	114	131	120
		1.5 ATA Series (n-9)		
Control (first O_2 module)	126	110	119	108
Exposure (final O_2 module)	124	121	99	90

All pressures in cm H_2O.

pressure increased. In contrast, at 1.5 ATA, inspiratory pressure increased while expiratory pressure decreased. It is possible that the difference in duration of these exposures (mean durations: 9.73 hr. at 2.0 ATA; 17.65 hr. at 1.5 ATA) influenced these results. Results of the control exposures and statistical analyses will have to be completed before the changes can be interpreted. Control exposures of 20-hour duration are scheduled to be performed later this year.

Maximal force and duration of handgrip did not change appreciably during the 3.0 ATA exposure series. Results for the 2.0 ATA and 1.5 ATA exposure series are summarized in Table 10. Again, the results are not consistent across the two exposure series. At 2.0 ATA, both maximum handgrip and its duration declined slightly during the exposure, while at 1.5 ATA, they both increased. These results can also be interpreted only in the light of control measurements and full statistical analysis.

PULMONARY EFFECTS

Pulmonary function was evaluated only before and after exposure in the previous series of oxygen exposures at 3.0 ATA; because it was anticipated that decrements would be small and that the time required for pulmonary measurements during exposure could be better used to monitor CNS effects. The later onset and lesser magnitude of CNS effects in the present series of exposures at 2.0 and 1.5 ATA allowed continuation of oxygen breathing until pulmonary effects became dominant. In contrast to the 3.0 ATA series in which almost all subject exposures were continued to 3.5 hours, the end-exposure points for all subjects at 2.0 ATA and all but two at 1.5 ATA were determined by degree of decrement in pulmonary function and/or severity of pulmonary symptoms.

Spirometric Measurements of Pulmonary Function during Oxygen Exposure at 2.0 and 1.5 ATA

At 2.0 ATA where the average exposure duration was 9.7 hours (Table 2), performance of initial and final 2.5-hour measurement modules in each of two subjects (Fig. 6) left little time for monitoring pulmonary function between modules. Since rate of development of pulmonary oxygen poisoning in man at 2.0 ATA was known from a previous series of experiments (5,18), this compromise in experiment design was accepted to provide time for measurement of oxygen effects on several organs and functions that were not studied previously. The longer exposure durations at 1.5 ATA (mean 17.7 hours, Table 2) allowed time for periodic monitoring of pulmonary function in addition to the 2.5-hour modules (Fig. 8).

Exposure at 2.0 ATA. Average values (N=7) of lung volumes and flow rates measured early (1.1 hours) and late (9.0 hours) during oxygen exposure at 2.0 ATA are summarized in Table 11). The standard symbols for pulmonary function measurements are defined in an appendix glossary. Statistically significant

TABLE 10.

MAXIMUM HANDGRIP FORCE AND DURATION
OF SUSTAINED 80% OF MAXIMUM HANDGRIP FORCE

(Mean Values)

MEASUREMENT	MAXIMUM HANDGRIP	DURATION OF 80% MAX. HG
	2.0 ATA Series (n-6)	
Oxygen Module 1	55	26
Oxygen Module 2	49	22
	1.5 ATA Series (n-9)	
Oxygen Module 1	47	38
Oxygen Module 2	50	45

Maximum handgrip measured in kg.
Duration of 80% maximum handgrip (endurance) measured in sec.

TABLE 11.

LUNG VOLUMES AND FLOW RATES DURING OXYGEN EXPOSURE AT 2.0 ATA
(Mean values ± SD)

Parameter	Number of Subjects	Oxygen Exposure Time 1.1 hours	Oxygen Exposure Time 9.0 hours	Mean Difference
		Mean ± SD	Mean ± SD	
FEVC (L)	7	5.32 ± 0.82	4.32 ± 0.90	-1.00*
FEV_1 (L)	6	3.79 ± 0.33	3.18 ± 0.77	-0.61
PEFR (L/sec)	6	8.02 ± 2.75	5.86 ± 1.31	-2.16
FEF(25%-75%) (L/sec)	6	2.75 ± 0.65	2.43 ± 0.84	-0.32
FEV_1/FEVC	6	0.69 ± 0.08	0.71 ± 0.07	+0.02
FIVC (L)	7	5.38 ± 0.89	4.37 ± 1.26	-1.01*
FIV_1 (L)	6	4.48 ± 0.60	3.52 ± 0.99	-0.96
PIFR (L/sec)	6	6.32 ± 0.98	4.89 ± 1.26	-1.43*
FIF 50% (L/sec)	6	5.64 ± 1.02	4.18 ± 1.26	-1.46*
FIV_1/FIVC	6	0.79 ± 0.07	0.75 ± 0.16	-0.04
PEFR/PIFR	6	1.29 ± 0.46	1.27 ± 0.42	-0.02
SVC (L)	7	5.53 ± 0.99	4.46 ± 1.21	-1.07*
TV (L)	7	0.85 ± 0.36	0.77 ± 0.28	-0.08
IC (L)	7	2.99 ± 0.79	2.42 ± 0.61	-0.57
IRV (L)	7	2.14 ± 0.82	1.65 ± 0.71	-0.49
ERV (L)	7	2.53 ± 0.88	2.04 ± 0.93	-0.49

* Statistically significant difference ($p \leq 0.05$, paired t test).

decrements occurred in the forced expiratory and inspiratory vital capacities (FEVC and FIVC), peak inspiratory flow rate (PIFR), forced inspiratory flow at 50% of vital capacity (FIF_{50}), and slow vital capacity (SVC). Expressed as percents of early exposure control values, the average decrements are: FEVC -18.8%, FIVC -18.8%, PIFR -26.5%, FIF_{50} -31.0%, and SVC -19.3%.

Exposure at 1.5 ATA. Average values (N=9) of lung volumes and flow rates measured during oxygen breathing at 1.5 ATA are summarized in Table 12. Results are similar to those obtained at 2.0 ATA except that additional significant changes were detected in the larger subject group. Significant decrements were found in FEVC, FEV_1, PEFR, FEV_1/FEVC, FIVC, FIV_1, PIFR, FIF_{50}, SVC, inspiratory capacity (IC), and inspiratory reserve volume (IRV). The earliest significant changes occurred at an average exposure duration of 11.8 hours. Indices that were sufficiently sensitive to detect an oxygen effect on pulmonary function at this time included FEVC, FEV_1, PEFR, FIVC, FIV_1, and PIFR. Percent changes from early exposure control values for the last exposure measurements of the parameters that decreased significantly are: FEVC -19.7%, FEV_1 -14.1%, PEFR -24.9%, FIVC -21.5%, FIV_1 -23.3%, PIFR -22.9%, FIF_{50} -22.5%, SVC -21.4%, IC -25.4%, and IRV -32.4%. Average decrements for corresponding pulmonary function indices are generally similar at both 1.5 and 2.0 ATA.

Average values of FEVC and FIVC are plotted against duration of oxygen exposure at 1.5 ATA in Fig. 19A, and corresponding plots of PEFR and PIFR are shown in Fig. 19B. Both FEVC and FIVC have smoothly progressive decrements and nearly parallel curves during oxygen exposure. Peak expiratory and inspiratory flow rates on the other hand, appear to converge slightly during the last 4 hours of exposure.

Comparison with Previous Data and Predictions. Average FEVC data from the present experiments are compared in Fig. 20 with previous vital capacity measurements at 2.0 ATA (5) and with previous predictions of vital capacity responses to oxygen exposure at 1.5 ATA (Fig. 20). All data are expressed as percent decrease in vital capacity relative to duration of oxygen breathing at 2.0 or 1.5 ATA. The curve on the left is drawn smoothly through previous vital capacity data in eleven subjects and extended to include the point (X) from the present series of seven subjects. Data from both groups of subjects are in good general agreement.

The predictive curve on the right is based on the same data used to derive the hyperbolic pulmonary oxygen tolerance curves shown in Fig. 1. The points (o) plotted below the curve represent average measurements in nine subjects exposed to oxygen at 1.5 ATA (Table 12). The actual measurements are within 1% of the predictive curve for vital capacity changes as great as -12% and within 3% of the curve for larger changes. The present data will permit further refinement of the predictive curves to obtain even closer agreement.

TABLE 12.

LUNG VOLUMES AND FLOW RATES DURING OXYGEN EXPOSURE AT 1.5 ATA
(Mean values ± SD in 9 subjects)

Parameter	Mean Exposure Time (hours) 0.15[1]	3.8	7.9	11.8	14.1	16.7	Final[2] 17.5 ± 0.8
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
FEVC (L)	5.63 ± 0.90	5.56 ± 0.85	5.36 ± 0.71	5.09* ± 0.86	4.95* ± 0.81	4.61* ± 1.23	4.52* ± 1.15
FEV_1 (L)	4.18 ± 0.61	4.19 ± 0.52	3.96 ± 0.62	3.74* ± 0.65	3.77* ± 0.60	3.56* ± 0.81	3.59* ± 0.84
PEFR (L/sec)	8.06 ± 1.38	7.97 ± 0.99	7.22 ± 1.78	6.50* ± 1.36	6.27* ± 1.62	6.04* ± 1.63	6.05* ± 1.79
FEF(25%-75%) (L/sec)	3.53 ± 0.90	3.64 ± 0.92	3.41 ± 0.91	3.14 ± 0.93	3.34 ± 0.81	3.28 ± 0.90	3.37 ± 0.85
FEV_1/FEVC	0.75 ± 0.07	0.76 ± 0.08	0.74 ± 0.08	0.74 ± 0.09	0.76 ± 0.08	0.78 ± 0.09	0.80* ± 0.05
FIVC (L)	5.71 ± 0.87	5.58 ± 0.85	5.44 ± 0.73	5.16* ± 0.84	5.02* ± 0.86	4.73* ± 1.24	4.48* ± 1.06
FIV_1 (L)	4.29 ± 1.14	4.00 ± 0.90	4.00 ± 0.98	3.58* ± 0.53	3.59* ± 1.09	3.29* ± 1.23	3.29* ± 1.08
PIFR (L/sec)	6.19 ± 1.72	5.41 ± 1.45	5.58 ± 1.59	4.96* ± 1.11	4.90* ± 1.50	4.78* ± 1.52	4.77* ± 1.63
PIF 50% (L/sec)	5.07 ± 1.51	4.93 ± 1.53	5.02 ± 1.44	4.29 ± 0.82	4.32 ± 1.32	3.98* ± 1.45	3.93* ± 1.58
FIV_1/FIVC	0.75 ± 0.13	0.72 ± 0.13	0.73 ± 0.13	0.70 ± 0.07	0.71 ± 0.13	0.70 ± 0.16	0.73 ± 0.13
PEFR/PIFR	1.36 ± 0.29	1.55 ± 0.34	1.35 ± 0.40	1.36 ± 0.37	1.34 ± 0.38	1.32 ± 0.37	1.32 ± 0.35
SVC (L)	5.75 ± 0.69	5.70 ± 0.67	5.46 ± 0.63	5.30 ± 0.84	4.93* ± 0.96	4.74* ± 1.16	4.52* ± 1.38
TV (L)	0.83 ± 0.13	0.76 ± 0.12	0.74 ± 0.11	0.75 ± 0.11	0.84 ± 0.15	0.73 ± 0.14	0.79 ± 0.20
IC (L)	3.30 ± 0.89	3.24 ± 0.47	3.07 ± 0.60	2.89 ± 0.75	2.72* ± 0.63	2.45* ± 0.84	2.46* ± 1.02
IRV (L)	2.47 ± 0.82	2.47 ± 0.42	2.33 ± 0.64	2.15 ± 0.81	1.89* ± 0.61	1.72* ± 0.84	1.67* ± 0.89
ERV (L)	2.43 ± 0.51	2.46 ± 0.46	2.39 ± 0.39	2.40 ± 0.34	2.21 ± 0.50	2.29 ± 0.56	2.07 ± 0.46

1 Control for exposure at 1.5 ATA.
2 Last measurement during oxygen exposure.
* Statistically significant difference from control value ($p \leq 0.05$).

FIGURE 19a.

RATES OF DECREASE IN FEVC AND FIVC DURING OXYGEN EXPOSURES AT 1.5 ATA.

(mean values in 9 subjects)

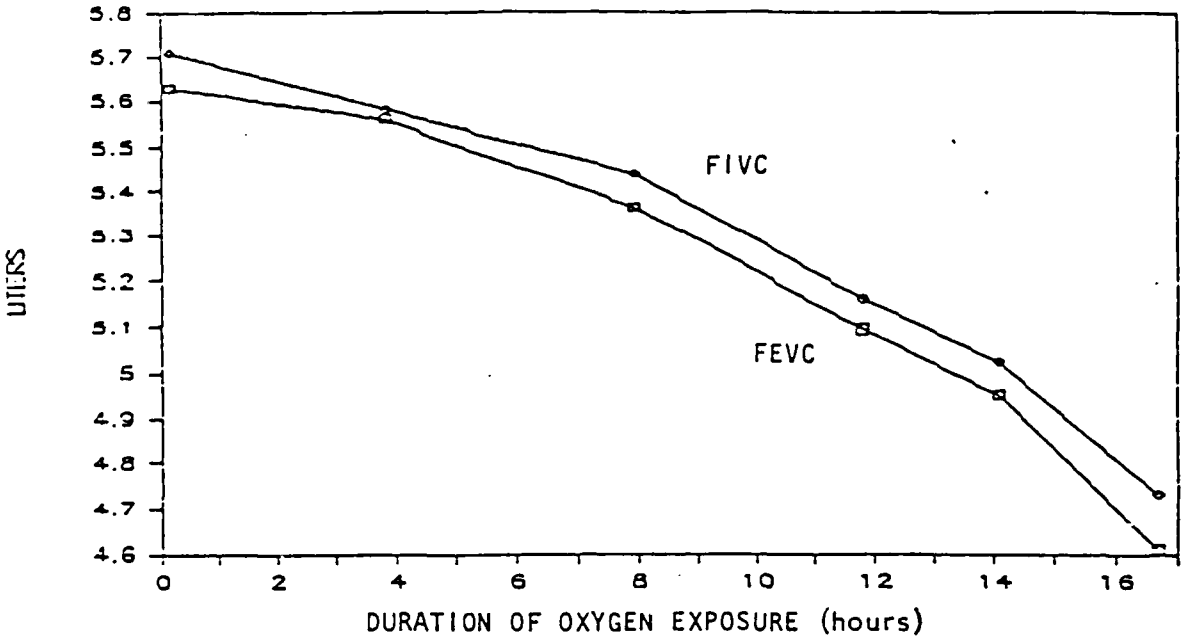


FIGURE 19b.

RATES OF DECREASE IN PEFR AND PIFR DURING OXYGEN EXPOSURES AT 1.5 ATA.

(mean values in 9 subjects)

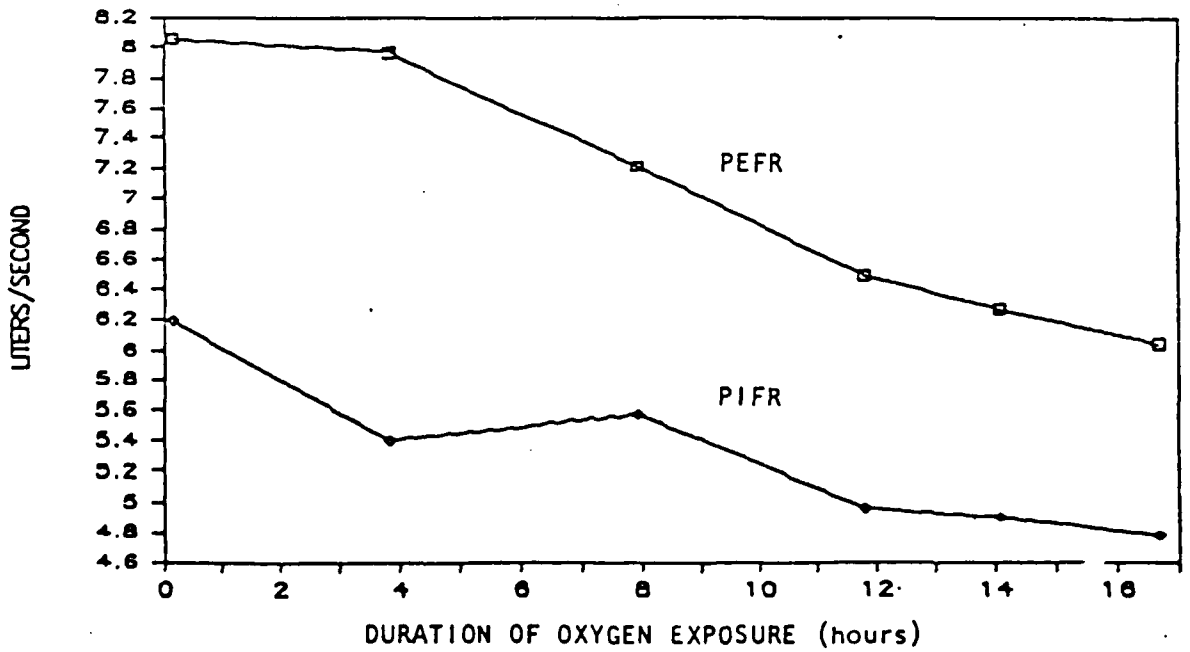
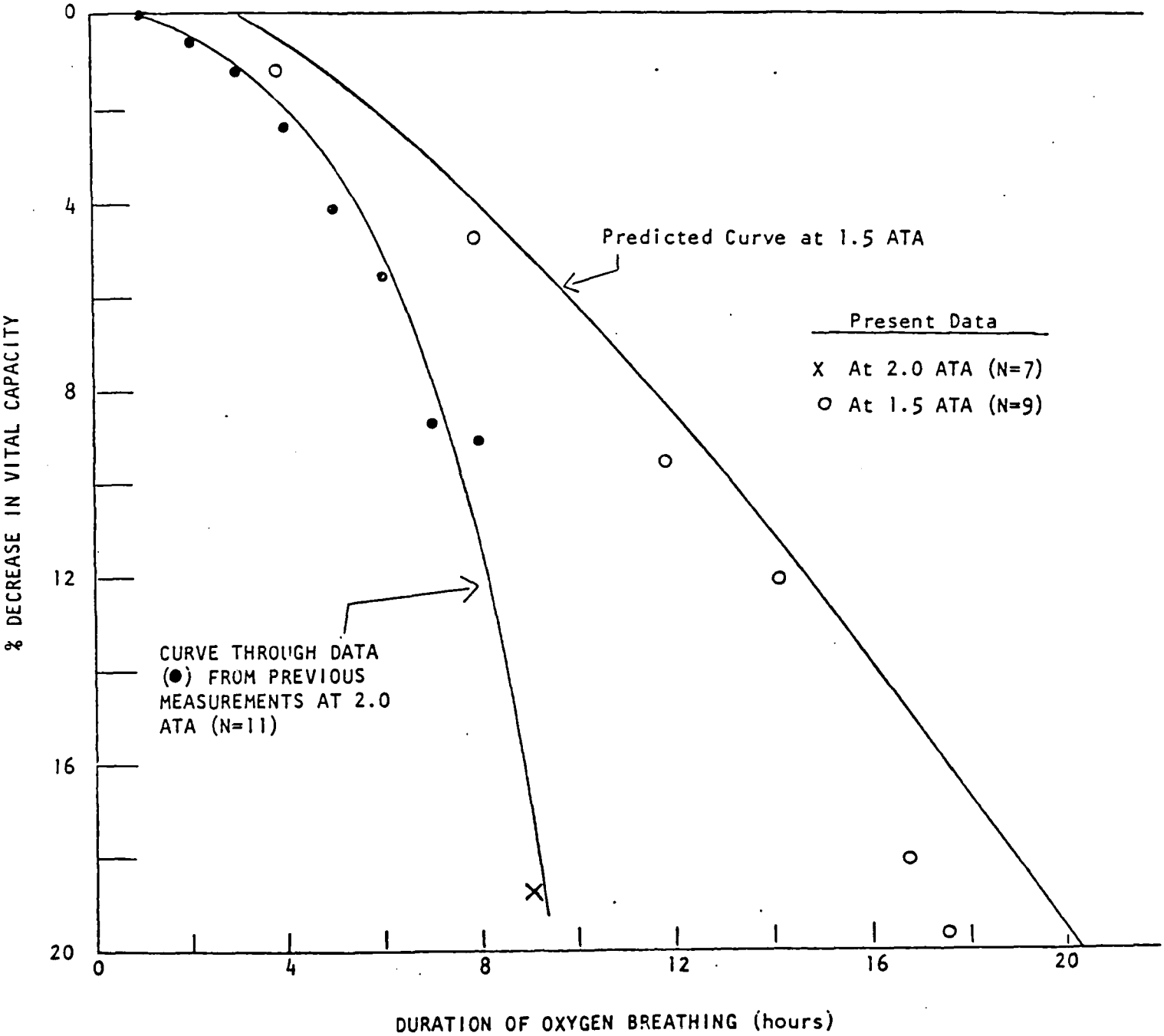


FIGURE 20.

RATE OF DECREASE IN VITAL CAPACITY DURING OXYGEN BREATHING AT 2.0 AND 1.5 ATA. COMPARISON OF PRESENT DATA WITH PREVIOUS MEASUREMENTS AT 2.0 ATA AND PREDICTIONS FOR 1.5 ATA.



Recovery of Lung Volumes and Flow Rates after Oxygen Exposure at 2.0 and 1.5 ATA

After Oxygen Exposure at 2.0 ATA. Average values of lung volumes and flow rates after oxygen exposure at 2.0 ATA are summarized in Table 13. Early recovery measurements at 4.0 and 11.9 hours post-exposure were obtained in five subjects, while later recovery data represent averages for seven subjects. Average values in five subjects characteristically indicate a further decrement in pulmonary function between 4.0 and 11.9 hours post-exposure. Average post-exposure values for FEVC are shown as an example of this phenomenon (Fig. 21). Similar results were found previously after oxygen exposure at 2.0 ATA in a group of ten subjects (5). In all seven subjects of the present group, none of the lung volumes or flow rates differed significantly from pre-exposure control values by the first post-exposure day. Average values returned to control levels within 2 to 4 days post-exposure.

After Oxygen Exposure at 1.5 ATA. Table 14 contains average values of lung volumes and flow rates obtained in nine subjects after oxygen exposure at 1.5 ATA. With the single exception of PIFR, all of the lung volumes and flow rates that decreased significantly during oxygen exposure (Table 12) remained depressed at 3.6 hours post-exposure. Indices that still had significant decrements at 13.0 hours after exposure termination were FEVC, FEV_1, PEFR, FIV_1, FIF_{50}, and SVC, while FIVC, IC, and IRV were no longer different from pre-exposure control values. All indices returned to control levels by one day post-exposure. Although the decrements in lung volumes and flow rates caused by oxygen exposure for 17.7 hours at 1.5 ATA (Table 12) were equivalent in magnitude to those caused by exposure for 9.7 hours at 2.0 ATA, the continued progression of functional deficit found after exposure at 2.0 ATA (Fig. 21) did not occur after exposure at 1.5 ATA (Fig. 22).

Other Measurements of Pulmonary Function at 1.0 ATA after Oxygen Exposure at 2.0 and 1.5 ATA

Density dependence of flow rates, closing volumes, and carbon monoxide diffusing capacities were measured at 1.0 ATA at regular intervals after oxygen exposure at 2.0 or 1.5 ATA. Average values obtained after 2.0 ATA exposure are summarized in Table 15 and those measured after 1.5 ATA exposure are in Table 16.

Density Dependence of Flow Rates. As an index of density effect on expiratory flow, maximum expiratory flow rates while breathing air were compared with similar efforts after 3 full breaths of 80% He-20% O_2. The difference between maximum flow rates for the 2 gases at 50% of the vital capacity ($\Delta\dot{V}max_{50}$) is narrowed in disease states that increase resistance to flow through peripheral airways (33). Although previous measurements in five subjects indicated that $\Delta\dot{V}max_{50}$ was reduced after oxygen

TABLE 13.

RECOVERY OF LUNG VOLUMES AND FLOW RATES AFTER OXYGEN EXPOSURE AT 2.0 ATA
(Mean values ± SD in 7 subjects)

Parameter	Pre-exposure Control[1]	Post-exposure Interval							
		4.0 hrs[2]	11.9 hrs[2]	1 day	2 days	3 days	4 days	9 days	18 days
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
FEVC (L)	5.46 ±0.84	4.62 ±0.93	4.40 ±1.02	5.01 ±0.69	5.30 ±0.73	5.47 ±0.95	5.45 ±0.88	5.67 ±0.94	5.64 ±0.90
FEV_1 (L)	4.32 ±0.29	3.83 ±0.86	3.64 ±0.76	3.85 ±0.55	4.14 ±0.22	4.29 ±0.30	4.33 ±0.29	4.49 ±0.32	4.47 ±0.44
PEFR (L/sec)	10.22 ±2.26	7.98 ±2.21	8.41 ±2.13	8.87 ±1.56	9.66 ±1.09	10.50 ±2.42	11.22 ±3.76	10.62 ±1.04	10.12 ±1.27
FEF(25%-75%) (L/sec)	4.15 ±0.86	4.15 ±1.35	3.94 ±0.78	3.67 ±1.08	3.95 ±1.14	4.22 ±1.15	4.18 ±1.17	4.39 ±1.01	4.35 ±1.33
FEV_1/FEVC	0.80 ±0.08	0.83 ±0.11	0.83 ±0.05	0.78 ±0.12	0.79 ±0.10	0.80 ±0.10	0.81 ±0.09	0.80 ±0.08	0.80 ±0.09
FIVC (L)	5.39 ±0.83	4.56 ±0.83	4.39* ±1.06	4.97 ±0.57	5.29 ±0.76	5.47 ±0.95	5.43 ±0.90	5.61 ±0.89	5.62 ±0.89
FIV_1 (L)	4.51 ±0.77	3.59 ±0.89	2.92* ±0.91	3.98 ±0.81	4.17 ±0.99	4.24 ±0.93	4.49 ±0.90	4.69 ±0.61	4.46 ±0.72
PIFR (L/sec)	7.60 ±2.04	5.62 ±1.71	4.37* ±1.21	6.65 ±2.14	6.85 ±2.33	7.33 ±1.98	7.78 ±1.78	8.14 ±1.26	8.02 ±0.99
PIF 50% (L/sec)	6.55 ±1.82	5.13 ±1.82	3.11* ±1.44	6.08 ±2.09	6.21 ±2.54	6.20 ±2.22	6.43 ±2.51	6.88 ±2.09	7.22 ±1.65
FIV_1/FIVC	0.84 ±0.08	0.79 ±0.16	0.67 ±0.15	0.80 ±0.11	0.78 ±0.14	0.78 ±0.14	0.83 ±0.11	0.85 ±0.11	0.81 ±0.15
PEFR/PIFR	1.40 ±0.26	1.44 ±0.08	2.02 ±0.77	1.52 ±0.71	1.56 ±0.58	1.49 ±0.34	1.47 ±0.42	1.33 ±0.26	1.27 ±0.18
SVC (L)	5.63 ±0.88	4.58* ±1.04	4.19* ±1.24	5.20 ±0.67	5.42 ±0.83	5.57 ±0.85	-	-	-
TV (L)	0.76 ±0.18	0.77 ±0.35	0.66 ±0.26	0.75 ±0.21	0.85 ±0.23	1.03 ±0.62	-	-	-
IC (L)	3.07 ±1.04	2.20 ±0.93	2.73 ±0.71	3.09 ±0.52	3.00 ±0.76	2.90 ±1.35	-	-	-
IRV (L)	2.31 ±1.00	1.43 ±0.67	2.07 ±0.64	2.34 ±0.51	2.15 ±0.83	2.50 ±0.91	-	-	-
ERV (L)	2.55 ±0.89	2.37 ±0.95	1.46* ±0.58	2.11 ±0.67	2.42 ±0.90	2.22 ±0.66	-	-	-

1 Average of measurements obtained at 4 different times.
2 Measurements in 5 subjects
* Statistically different from pre-exposure control value ($p \leq 0.05$).

FIGURE 21.

RECOVERY OF FEVC AFTER EXPOSURE AT 2.0 ATA

(mean values in 5 subjects)

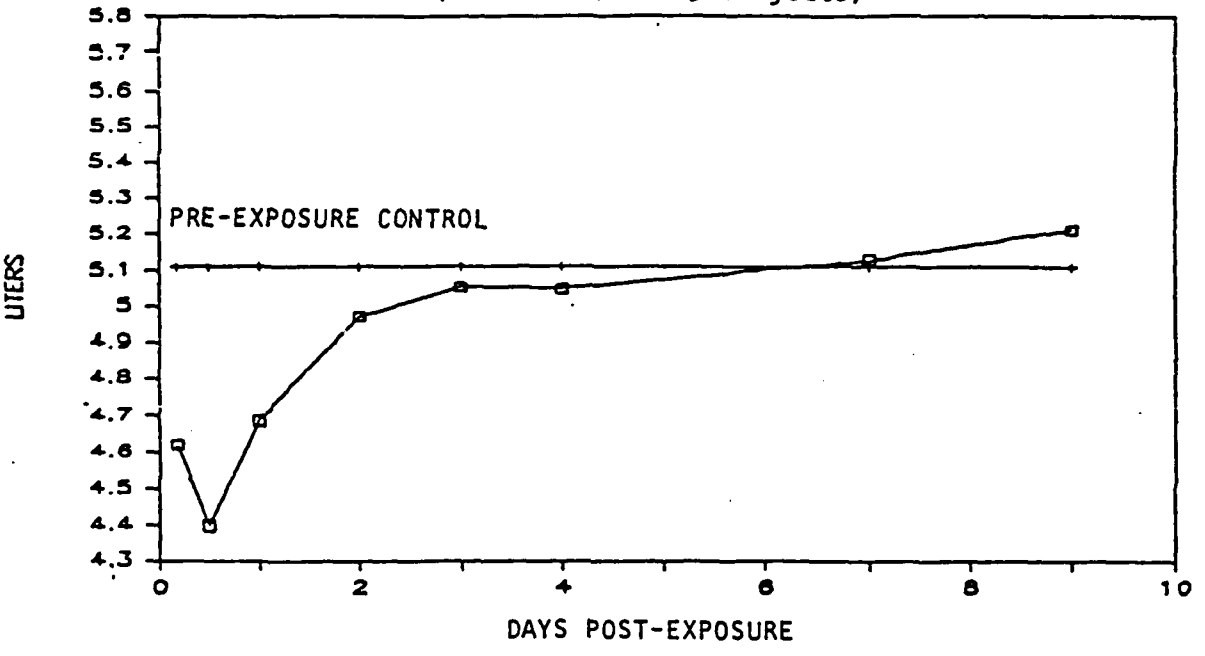


TABLE 14.

RECOVERY OF LUNG VOLUMES AND FLOW RATES AFTER OXYGEN EXPOSURE AT 1.5 ATA
(Mean values ± SD in 9 subjects)

Parameter	Pre-exposure Control[1]	Post-exposure Interval				
		3.6 hrs	13.0 hrs	1 day	2 days	7-8 days
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
FEVC (L)	5.55 ± 0.69	4.82* ± 0.92	5.08* ± 0.61	5.63 ± 0.72	5.63 ± 0.70	5.68 ± 0.74
FEV_1 (L)	4.58 ± 0.46	4.16* ± 0.79	4.15* ± 0.60	4.61 ± 0.57	4.59 ± 0.57	4.61 ± 0.49
PEFR (L/sec)	11.26 ± 1.19	9.58* ± 1.90	8.92* ± 2.21	11.29 ± 1.33	11.34 ± 1.55	11.45 ± 1.90
FEF(25%-75%) (L/sec)	4.72 ± 0.89	4.91 ± 1.[illegible]	4.25 ± 1.32	4.70 ± 1.13	4.72 ± 1.35	4.52 ± 0.85
FEV_1/FEVC	0.83 ± 0.06	0.88 ± 0.09	0.82 ± 0.09	0.82 ± 0.06	0.82 ± 0.06	0.81 ± 0.05
FIVC (L)	5.23 ± 0.71	4.71* ± 1.31	5.10 ± 0.63	5.59 ± 0.65	5.51 ± 0.65	5.60 ± 0.64
FIV_1 (L)	4.59 ± 0.83	3.64* ± 0.83	3.74* ± 0.90	4.46 ± 1.14	4.73 ± 0.82	4.60 ± 0.98
PIFR (L/sec)	7.65 ± 1.91	5.80 ± 1.67	5.59 ± 1.67	7.30 ± 1.95	7.61 ± 2.01	7.44 ± 2.02
FIF 50% (L/sec)	6.71 ± 1.80	4.34* ± 1.54	4.42* ± 1.88	6.48 ± 1.85	6.31 ± 1.41	6.55 ± 2.22
FIV_1/FIVC	0.83 ± 0.09	0.78 ± 0.14	0.73 ± 0.16	0.79 ± 0.16	0.85 ± 0.09	0.82 ± 0.12
PEFR/PIFR	1.58 ± 0.35	1.57 ± 0.15	1.66 ± 0.35	1.66 ± 0.55	1.57 ± 0.41	1.61 ± 0.36
SVC (L)	5.66 ± 0.73	4.94* ± 0.87	5.24* ± 0.63	5.79 ± 0.67	5.78 ± 0.71	5.78 ± 0.56
TV (L)	0.80 ± 0.11	0.78 ± 0.14	0.81 ± 0.15	0.78 ± 0.18	0.82 ± 0.14	0.72 ± 0.16
IC (L)	3.40 ± 0.78	2.84* ± 0.51	3.14 ± 0.59	3.48 ± 0.57	3.63 ± 0.61	3.44 ± 0.92
IRV (L)	2.60 ± 0.74	2.06* ± 0.57	2.32 ± 0.53	2.69 ± 0.67	2.81 ± 0.56	2.72 ± 0.92
ERV (L)	2.26 ± 0.25	2.10 ± 0.46	2.11 ± 0.40	2.32 ± 0.40	2.15 ± 0.43	2.34 ± 0.46

[1] Average of measurements obtained at 4 different times.
* Statistically significant difference from control value ($p \leq 0.05$).

FIGURE 22.

RECOVERY OF FEVC AFTER OXYGEN EXPOSURE AT 1.5 ATA

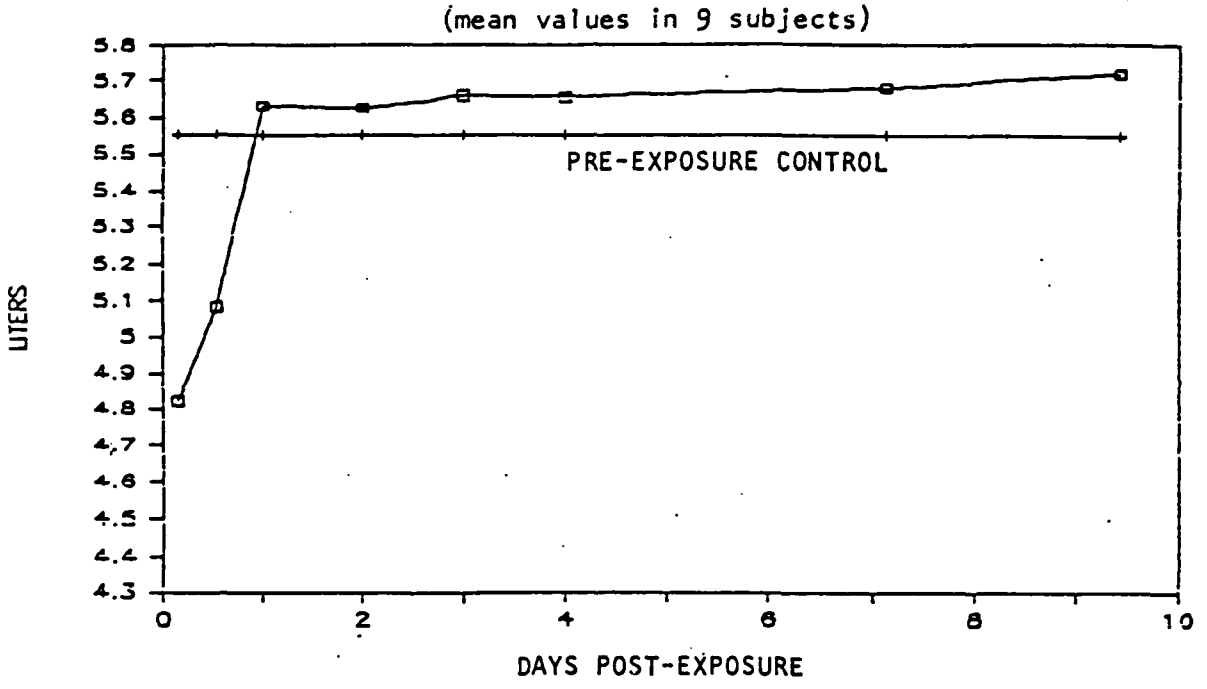


TABLE 15.

RECOVERY OF PULMONARY FUNCTION AFTER OXYGEN EXPOSURE AT 2.0 ATA
(Mean values ± SD in 7 subjects)

Parameter	Pre-exposure Control[1]	Post-exposure Interval: 4.0 hrs[2]	11.9 hrs[2]	1 day	2 days	3 days	4 days	9 days	18 days
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
$\Delta \dot{V}_{max50}$ (L)	1.75 ±0.80	2.12 ±0.45	1.22 ±0.91	1.54 ±1.00	2.14 ±0.75	1.52 ±0.96	1.82 ±0.59	2.02 ±1.14	2.32 ±0.79
% $\Delta \dot{V}_{max50}$	35.2 ±13.8	60.0 ±45.3	24.6 ±16.4	32.0 ±13.9	50.4 ±16.6	32.3 ±17.7	38.0 ±12.3	37.0 ±13.0	42.0 ± 5.2
$V_{iso\dot{V}}$ (L)	0.74 ±0.20	0.83 ±0.54	-	0.86 ±0.54	0.97 ±0.44	1.22 ±0.65	0.88 ±0.41	1.06 ±0.80	0.94 ±0.44
% $V_{iso\dot{V}}$	13.4 ±2.8	17.8 ±11.2	-	16.4 ±8.9	18.8 ±9.5	22.0 ±8.6	15.8 ±5.6	18.2 ±12.2	16.7 ±6.9
CV (L)	0.63 ±0.21	1.03 ±0.64	-	1.02 ±0.64	1.05 ±0.64	1.02 ±0.75	1.01 ±0.73	0.83 ±0.68	0.53 ±0.35
% CV/VC	14. ±5.	32. ±22.	-	24. ±17.	23. ±15.	22. ±17.	21. ±15.	17. ±14.	10. ±5.
DLCO (ml/min/torr)	35.5 ±8.9	28.0 ±3.7	28.4 ±4.2	31.1* ±7.2	30.9* ±7.0	30.9* ±7.2	31.4* ±8.4	30.3* ±6.8	32.7 ±8.5
DL/V_A (ml/min/torr/L)	5.3 ±1.1	4.8 ±0.7	5.1 ±1.0	4.7 ±0.6	4.7 ±0.9	4.6 ±0.7	4.5 ±0.6	4.4 ±0.3	4.6 ±0.6

1 Average of measurements obtained at 4 different times.
2 Measurements in 5 subjects
* Statistically different from pre-exposure control value ($p \leq 0.05$).

TABLE 16.

RECOVERY OF PULMONARY FUNCTION AFTER OXYGEN EXPOSURE AT 1.5 ATA
(Mean values ± SD in 9 subjects)

Parameter	Pre-exposure Control[1]	Post-exposure Interval 3.6 hrs	13.0 hrs	1 day	2 days	7-8 days
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
$\Delta \dot{V}_{max50}$ (L)	2.37 ± 0.93	1.29 ± 0.89	1.95 ± 1.04	2.25 ± 1.00	2.67 ± 1.52	1.89 ± 1.01
% $\Delta \dot{V}_{max50}$	45.2 ±10.3	25.3 ±16.3	42.4 ±26.8	42.1 ±11.2	49.0 ±11.1	36.7 ±15.1
$V_{iso}\dot{V}$ (L)	0.79 ± 0.30	0.67 ± 0.48	0.54 ± 0.19	0.75 ± 0.27	0.75 ± 0.32	0.75 ± 0.24
% $V_{iso}\dot{V}$	13.9 ± 5.4	14.0 ±10.2	10.8 ± 4.2	13.5 ± 5.1	13.2 ± 4.9	12.8 ± 3.8
CV (L)	0.37 ± 0.17	0.42 ± 0.19	0.44 ± 0.42	0.46 ± 0.40	0.42 ± 0.38	0.37 ± 0.31
% CV/VC	7.6 ± 3.0	10.3 ± 4.5	9.4 ± 7.4	9.2 ± 7.0	7.9 ± 6.1	7.2 ± 4.9
DLCO (ml/min/torr)	32.5 ± 4.4	30.4 ± 4.1	28.9* ± 4.0	29.6 ± 3.5	30.2 ± 5.0	30.0 ± 4.8
DL/V_A (ml/min/torr/L)	4.6 ± 0.7	4.5 ± 0.8	4.3 ± 1.0	4.2* ± 0.7	4.4 ± 0.9	4.3 ± 0.7

[1] Average of measurements obtained at 4 different times.
* Statistically significant difference from pre-exposure control value ($p \leq 0.05$).

exposure for 3.5 hours at 3.0 ATA (1983 Report), no significant changes were found after much longer exposures at 2.0 or 1.5 ATA.

The lung volume at which flow rates on He-O_2 and air become equal (Viso$\dot{V}$) is also increased in disease states that increase peripheral airway resistance (33). No significant changes in Viso$\dot{V}$ were found after oxygen exposure at 2.0 or 1.5 ATA.

Closing Volumes. Single-breath nitrogen washout was used to measure closing volume (CV) as another index of small airway function before and after oxygen exposure. Although no statistically significant changes were found after either exposure series, average values (N=7) of CV nearly doubled after oxygen exposure at 2.0 ATA and then declined progressively to reach the pre-exposure control level at 11 days post-exposure (Fig. 23). Average CV (N=9) was also increased slightly after oxygen exposure at 1.5 ATA and returned to the control level at about 7 days post-exposure.

Carbon Monoxide Diffusing Capacity. Pulmonary diffusing capacity for carbon monoxide (DL_{CO}) was measured by the single breath method before and after oxygen exposure. Mean values in seven subjects after exposure at 2.0 ATA indicate a significant decrement from the pre-exposure control value of 35.5 ml CO/mmHg/min to 31.1 at one day post-exposure. Earlier measurements in five subjects (14) showed a non-significant decrease from a pre-exposure value of 31.1 to 28.0 and 28.4, respectively, at 4.0 and 11.9 hours post-exposure. In the larger group of seven subjects, DL_{CO} remained significantly reduced with little or no recovery at 2, 3, 4, and 9 days post-exposure (Fig. 24). By post-exposure day 17, the decrement in DL_{CO} was no longer statistically significant. Some subjects appeared to take longer than 17 days for full recovery of DL_{CO}. More detailed analysis of individual data will be required to determine the range of variability in rate of DL_{CO} recovery.

After oxygen exposure at 1.5 ATA, mean values in nine subjects again show a persistent post-exposure decrement in DL_{CO} (Table 16). However, the magnitude of decrement is smaller than that found after oxygen exposure at 2.0 ATA, and the change is statistically significant only at 13.0 hours post-exposure. It is noteworthy that 17.7 hours of oxygen breathing at 1.5 ATA appeared to cause a smaller decrease in DL_{CO} than 9.7 hours of exposure at 2.0 ATA, even though both oxygen exposures produced similar decrements in lung volumes and flow rates (Tables 11 and 12).

Lung Compliance. Static and dynamic compliance were measured before and after oxygen exposure at 2.0 and 1.5 ATA. Measurements at 4 hours after exposure termination at 2.0 ATA (Table 17) indicate a statistically significant 31% reduction in static lung compliance with return to the control level by 37 days post-exposure. Dynamic lung compliance at a rate of 15 breaths per minute was not significantly changed.

FIGURE 23.

RECOVERY OF CLOSING VOLUMES AFTER OXYGEN EXPOSURE AT 2.0 ATA

(mean values in 5 subjects)

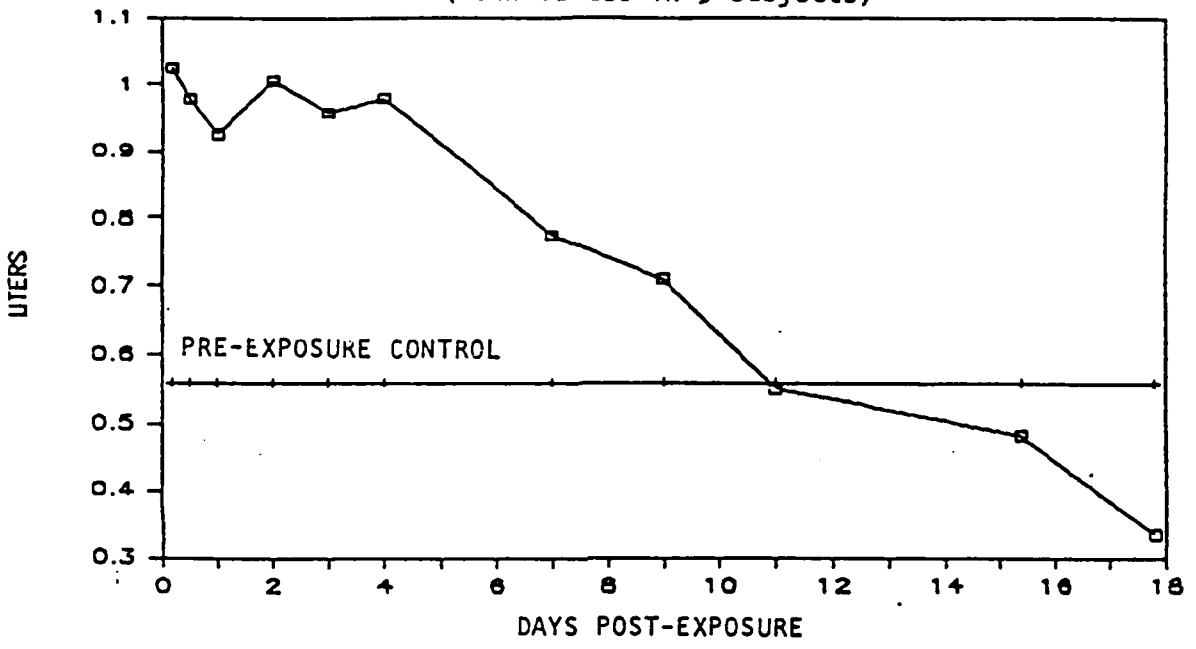


FIGURE 24.

RECOVERY OF $D_{L_{CO}}$ AFTER OXYGEN EXPOSURE AT 2.0 ATA

(mean values in 7 subjects)

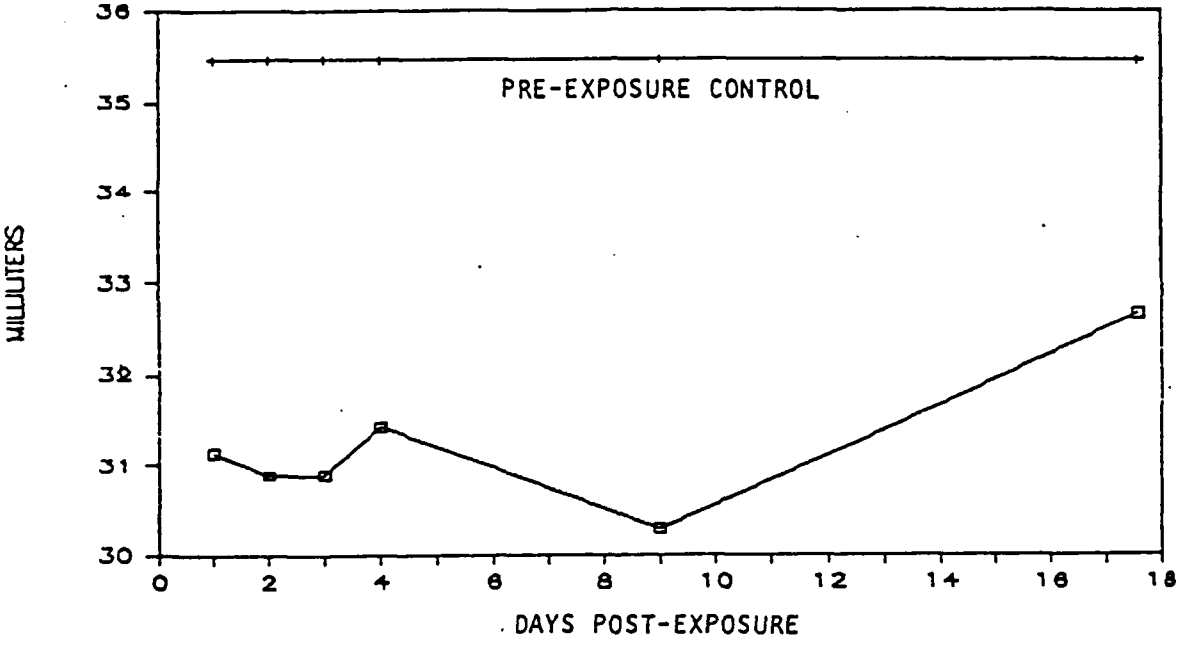


TABLE 17.

LUNG COMPLIANCE AND AIRWAY RESISTANCE
BEFORE AND AFTER OXYGEN EXPOSURE AT 2.0 ATA
(Mean values ± SD)

Parameter	Pre-exposure Control	Post-exposure Interval 4 hours	37 days
	Mean ± SD N = 6	Mean ± SD N = 6	Mean ± SD N = 5
C_L (L/cm H_2O)	0.26 ± 0.06	0.18* ± 0.03	0.24 ± 0.08
C_L15 (L/cm H_2O)	0.22 ± 0.05	0.17 ± 0.03	0.39 ± 0.34
R_{aw} (cm H_2O/L/sec)	2.01 ± 0.43	1.91 ± 0.56	1.81 ± 0.68

* Statistically significant difference from pre-exposure control ($p \leq 0.05$, paired t-test).

TABLE 18.

LUNG COMPLIANCE AND AIRWAY RESISTANCE
BEFORE AND AFTER OXYGEN EXPOSURE AT 1.5 ATA
(Mean values ± SD in 8 subjects)

Parameter	Pre-exposure[1] Control	Post-exposure Interval 3.5 hours	19 days
	Mean ± SD	Mean ± SD	Mean ± SD
C_L (L/cm H_2O)	0.24 ± 0.06	0.19 ± 0.04	0.27 ± 0.17
C_L15 (L/cm H_2O)	0.23 ± 0.05	0.22 ± 0.07	0.29 ± 0.22
C_L30 (L/cm H_2O)	0.19 ± 0.04	0.18 ± 0.04	0.19 ± 0.05
C_L60 (L/cm H_2O)	0.13 ± 0.03	0.13 ± 0.04	0.15 ± 0.06
R_{aw} (cm H_2O/L/sec)	1.69 ± 0.33	1.72 ± 1.04	1.70 ± 0.46

[1] Average of measurements obtained at 2 different times.
* Statistically significant difference from control value ($p \leq 0.05$).

Measurements after oxygen exposure at 1.5 ATA (Table 18) show a 21% reduction in average static compliance (0.24 to 0.19 l/cm H_2O) that was not statistically significant. Dynamic compliance at breathing rates of 15, 30, and 60 were not changed after oxygen exposure.

Airway Resistance. Average values of airway resistance measured in a body plethysmograph were obtained before and after oxygen exposure at 2.0 ATA (Table 17) and at 1.5 ATA (Table 18). Airway resistance was not changed after either exposure.

Arterial Blood Gases and Acid-Base State Before, During, and After Oxygen Exposure at 2.0 and 1.5 ATA

As a component of the overall evaluation of oxygen effects on pulmonary function, alveolar-arterial oxygen gradients [$(A\text{-}a)\Delta PO_2$] were measured at rest and during exercise while breathing air at 1.0 ATA before and after oxygen exposure. Under these conditions, the $(A\text{-}a)\Delta PO_2$ at rest is determined primarily by pulmonary ventilation-perfusion distribution. During exercise, mean pulmonary capillary transit time for red blood cells is greatly reduced, and $(A\text{-}a)\Delta PO_2$ is also influenced significantly by rate of oxygen diffusion across the alveolar-capillary membrane. In addition to the pre- and post-exposure measurements, early and late exposure values of $(A\text{-}a)\Delta PO_2$ during oxygen breathing at 2.0 or 1.5 ATA provided a measure of alveolar atelectasis during prolonged oxygen exposure. Arterial PCO_2, pH, and HCO_3^- were also measured as indices of acid-base state before, during, and after oxygen exposure.

Effects of Oxygen Exposure at 2.0 ATA. Average pre- and post-exposure values in seven subjects (Table 19) indicate that the 9.7-hour exposure at 2.0 ATA had no effect on $(A\text{-}a)\Delta PO_2$ at rest or during exercise. Average arterial PCO_2, pH, and HCO_3^- values were also remarkably similar before and after exposure. Average $(A\text{-}a)\Delta PO_2$ (N=4) during oxygen breathing at 2.0 ATA increased from 68 torr at 2.5 hours to 84 Torr at 9.9 hours of exposure. Individual values in one subject, whose $(A\text{-}a)\Delta PO_2$ increased from 65 to 225 torr, were consistent with cccurrence of alveolar atelectasis during oxygen exposure.

Effects of Oxygen Exposure at 1.5 ATA. Average $(A\text{-}a)\Delta PO_2$ during air breathing at rest in eight subjects (Table 20) increased by only 2.3 torr after oxygen exposure for 17.7 hours at 1.5 ATA. During exercise, average $(A\text{-}a)\Delta PO_2$ (N=7) increased from a control value of 12.5 torr to a post-exposure value of 20.4 torr, but the increment was not statistically significant. There were no significant changes in acid-base state. During oxygen breathing at 1.5 ATA, average $(A\text{-}a)\Delta PO_2$ (N=6) increased from 56 torr at 1.5 hours to 64 Torr at 15.3 hours of exposure. Individual values were consistent with alveolar atelectasis in only one subject whose $(A\text{-}a)\Delta PO_2$ increased from 81 to 153 torr during oxygen exposure.

TABLE 19.

ALVEOLAR PO_2 AND ARTERIAL PO_2, PCO_2, pH, AND HCO_3^-
BEFORE, DURING, AND AFTER OXYGEN EXPOSURE AT 2.0 ATA
(MEAN VALUES ± SD)

	Breathing Air at 1.0 ATA at Rest (N-7)		Breathing Air at 1.0 ATA During Exercise (N-7)	
	Pre-Exposure	Post-Exposure	Pre-Exposure	Post-Exposure
P_AO_2 (torr)	106.8 ± 4.9	100.2 ± 7.9	107.7 ± 2.4	107.7 ± 4.7
PaO_2 (torr)	91.9 ± 3.0	85.0 ± 12.2	90.3 ± 4.1	89.2 ± 6.6
(A-a)ΔPO_2(torr)	15.7 ± 7.1	15.2 ± 10.9	17.4 ± 5.0	17.9 ± 9.6
$PaCO_2$ (torr)	39.5 ± 2.8	41.2 ± 3.7	40.5 ± 1.0	39.5 ± 2.3
pHa	7.408 ± 0.028	7.391 ± 0.031	7.378 ± 0.017	7.385 ± 0.025
HCO_3^- (meq/L)	25.8 ± 1.5	25.9 ± 1.0	24.8 ± 1.1	24.4 ± 1.4

	Breathing Oxygen at 2.0 ATA at Rest (N-4)	
	Early Exposure	Late Exposure
P_AO_2	1442 ± 4	1439 ± 4
PaO_2	1374 ± 21	1355 ± 93
(A-a)ΔPO_2	68 ± 17	84 ± 94
$PaCO_2$	31.2 ± 3.9	34.0 ± 4.2
pHa	7.460 ± 0.021	7.410 ± 0.033
HCO_3^-	22.8 ± 1.9	2 ± 1.1

TABLE 20.

ALVEOLAR PO_2 AND ARTERIAL PO_2, PCO_2, pH, AND $HCO\bar{3}$
BEFORE, DURING, AND AFTER OXYGEN EXPOSURE AT 1.5 ATA
(MEAN VALUES ± SD)

	Breathing Air at 1.0 ATA at Rest (n-8)		Breathing Air at 1.0 ATA During Exercise (n-7)	
	Pre-Exposure	Post-Exposure	Pre-Exposure	Post-Exposure
P_AO_2 (torr)	107.6 ± 5.2	98.6 ± 10.5	106.5 ± 6.2	106.1 ± 5.3
PaO_2 (torr)	96.3 ± 7.5	85.0 ± 14.0	94.0 ± 7.8	85.7 ± 11.4
(A-a)ΔPO_2 (torr)	11.4 ± 4.3	13.7 ± 10.4	12.5 ± 4.8	20.4 ± 13.7
$PaCO_2$ (torr)	35.6 ± 3.6	37.9 ± 4.1	39.7 ± 3.6	37.2 ± 2.7
pHa	7.451 ± 0.031	7.422 ± 0.003	7.379 ± 0.022	7.390 ± 0.029
HCO_3^- (meq/L)	26.5 ± 2.4	26.3 ± 2.4	24.3 ± 2.8	23.3 ± 2.3

	Breathing Oxygen at 1.5 ATA at Rest (N-6)	
	Early Exposure	Late Exposure
P_AO_2	1056 ± 2	1059 ± 3
PaO_2	1000 ± 22	995 ± 45
(A-a)ΔPO_2	56 ± 20	64 ± 45
$PaCO_2$	37.2 ± 2.2	34.3 ± 2.8
pHa	7.401 ± 0.026	7.412 ± 0.023
HCO_3^-	23.9 ± 0.9	± 1.3

Bronchoalveolar Lavage after Oxygen Exposure

Bronchoalveolar lavage with sterile saline was performed about 8 to 10 hours after oxygen exposure in all seven subjects exposed at 2.0 ATA and in six of the ten subjects exposed at 1.5 ATA. Pre-exposure control lavages were performed in six subjects. The remaining subjects will have control lavages at a later date. Cell counts and differentials were performed immediately after collection of the lavage fluid. The remaining fluid was then concentrated and frozen for later analysis.

Normal values for total cells are about 14×10^6 with 0-1% polymorphonuclear leucocytes. Average values after oxygen exposure at 2.0 ATA (N=7) were 30.9×10^6 cells with 7.8% polys. After oxygen exposure at 1.5 ATA, average values in six subjects were 16.6×10^6 cells with 16.5% polys. The results indicate that a relative alveolar polycytosis persists for at least 8-10 hours after prolonged oxygen exposure at 2.0 or 1.5 ATA.

Effective Diffusion Area of the Lung (EDA)

A novel, noninvasive, breath-by-breath, on-line method of obtaining a measure postulated to be related to the sum of all cross-sectional areas available for diffusion of gases in/out of the lung (30), developed at this University, has been employed during the 1.5 ATA exposure series. The method is not currently applicable to use inside the chamber. Measurements were made before and after the oxygen exposures, both at rest and during mild exercise. Data processing and analysis will begin soon; results will especially be compared to those obtained with Diffusion Capacities measured by the single breath CO method.

CARDIOCIRCULATORY FUNCTIONS

Investigation of cardiovascular functions during the 2.0 ATA and 1.5 ATA oxygen exposures included monitoring and continuous recording of electrocardiogram, intermittent measurement of blood pressure by indwelling radial arterial catheter, and measurement of relative stroke volume changes by impedance cardiography (32). In addition, pulse rate response to "active standing" (31) (subject assuming erect position from supine position) was recorded at regular intervals during the exposure to assess autonomic influences upon circulatory reflex activity. As an overall index of hepatic blood flow and function, rate of indocyanine green dye disappearance from the arterial circulation after intravenous injection of a standardized dye bolus was measured pre-exposure and during early and late oxygen exposure.

Effects of Oxygen Exposure at 2.0 ATA

Circulatory and Electrocardiographic Responses at Rest. Circulatory responses (Table 21) at 2.6 hours of exposure to O_2 included a 16% decrease in the frequency of sinus node discharge. Since no measurable changes in stroke volume occurred, cardiac output decreased proportionately. During this initial period, mean arterial blood pressure increased slightly (not significant). Calculated systemic vascular resistance therefore also increased.

Electrocardiogram during this period demonstrated varying degrees of sinus bradycardia with sinus arrhythmia, but with no pauses that exceeded 2 seconds. Periods of nodal control were observed occasionally. No ectopy was noted.

With increased duration of exposure, the sinus rate accelerated slowly, in association with progressive decrease in the incidence of sinus arrythmia and periods of nodal control. No pauses occurred, and occasional premature atrial contractions were noted in this late period.

At an average exposure duration of 9.8 hours, sinus rate was significantly greater than the early exposure level and slightly exceeded the pre-exposure control value. Mean blood pressure was less than the early exposure level and nearly equal to the pre-exposure control, while stroke volume was about 9% less than the control value. Average cardiac output was greater than the early exposure value, but still about 6% less than the control value.

Responses to Active Standing. Pulse rate responses to active standing were evaluated pre-exposure and during early and late periods of exposure. Post-exposure measurements replaced the late exposure values in some subjects. No changes were detected in most subjects (Fig. 25). However, in one subject (C.H.), complete blunting of the normal tachycardic response to

TABLE 21

HEMODYNAMIC MEASUREMENTS DURING
OXYGEN EXPOSURE AT 2.0 ATA

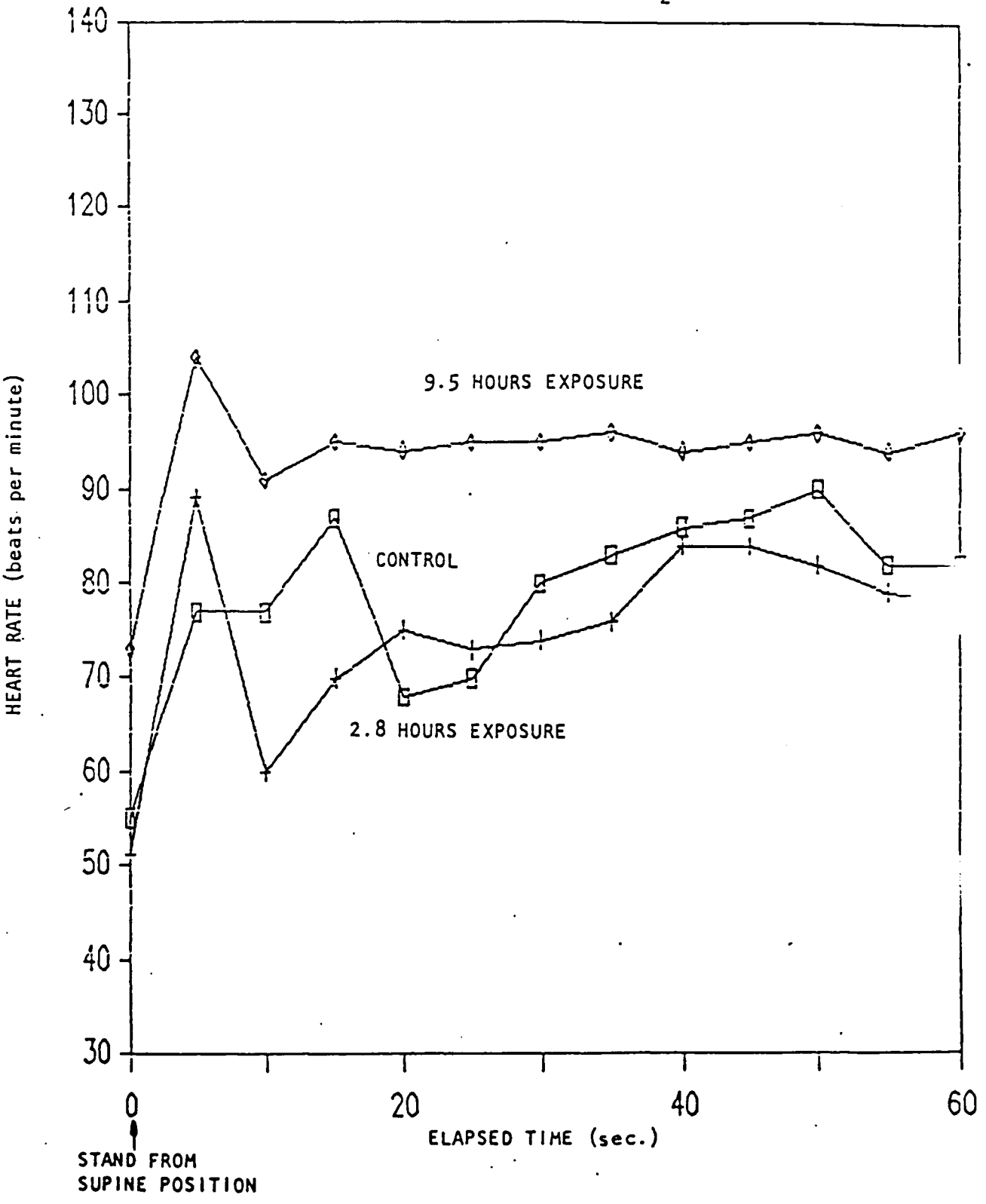
(Mean Values ± SD in 5 Supine Resting Subjects)

	Pre-exposure Control	Mean Exposure Time 2.6 Hours	9.8 Hours
Heart Rate (beats/min)	59.8 ± 10.7	50.2 ± 8.5	63.6* ± 14.4
Stroke Volume (% change)		+3.1 ± 11.8	-9.3 ± 32.6
Cardiac Output (% change)		-13.0 ± 15.4	-5.6 ±
Mean Arterial Blood Pressure (torr)	84.4 ± 14.3	97.0 ± 13.2	87.8 ± 20.7
Systemic Vascular Resistance (% change)		+35.3 ± 15.5	+23.9 ± 56.1

* Significantly greater than 2.6-hour value.

FIGURE 25.

HEART RATE RESPONSES TO RISING FROM SUPINE TO STANDING POSITION IN A TYPICAL SUBJECT (J.S.) BEFORE AND DURING O_2 EXPOSURE AT 2.0 ATA.



the maneuver occurred at 2.0 hours post-exposure (Fig. 26). While the tachycardic response was blunted, the blood pressure response remained intact, and the subject experienced no symptoms upon standing.

Similar blunting of the normal tachycardic response to standing may have occurred in 2 previous subjects (5) who experienced orthostatic fainting after oxygen exposure at 2.0 ATA. The previous subjects were not hydrated intravenously, while the present group received an infusion of 0.225% saline throughout the oxygen exposure. This important difference in the two subject groups may have allowed more adequate circulatory compensation for the blunted tachycardic response in subject C.H., making it possible for him to stand upright without fainting.

Hepatic Blood Flow and Function. Average curves (N=5) showing rates of fall in arterial dye concentration following an intravenous bolus of indocyanine green dye (Fig. 27) indicate that hepatic blood flow and function (as defined by this index) during both early and late oxygen exposure were not altered from the pre-exposure control state.

Effects of Oxygen Exposure at 1.5 ATA

Circulatory and Electrocardiographic Responses. At 2.2 hours of oxygen breathing, circulatory responses included parallel reductions in stroke volume and cardiac output of about 14% and 16%, respectively, with essentially no change in frequency of sinus node discharge (Table 22). In contrast to the finding at 2.0 ATA, mean arterial blood pressure decreased from 97.3 to 89.6 torr, and calculated systemic vascular resistance increased by about 12%. None of these changes were statistically significant.

The electrocardiogram changed little with respect to control during the 1.5 ATA exposures. Occasionally, premature atrial contractions were observed.

As the exposures progressed in time, changes in pulse rate comparable to the ones seen at 2.0 ATA were observed (progressive acceleration). The cardiac rhythm remained under sinus control, while increasing numbers of premature atrial and ventricular contractions appeared. The frequency of occurrence of such ectopic phenomena, which were probably caused by a generalized increase in myocardial excitability, remained largely at low levels. However, in one subject (M.M.), the oxygen exposure was terminated at 17.7 hours due to ventricular ectopy of progressive frequency and grade. In this case, continuous electrocardiographic monitoring demonstrated progressive disappearance of ectopy after exposure termination, with complete absence of ectopic beats by 6 hours post-exposure.

FIGURE 26.

HEART RATE RESPONSES TO RISING FROM SUPINE TO STANDING POSITION IN SUBJECT (C.H.) BEFORE, DURING, AND AFTER O_2 EXPOSURE AT 2.0 ATA.

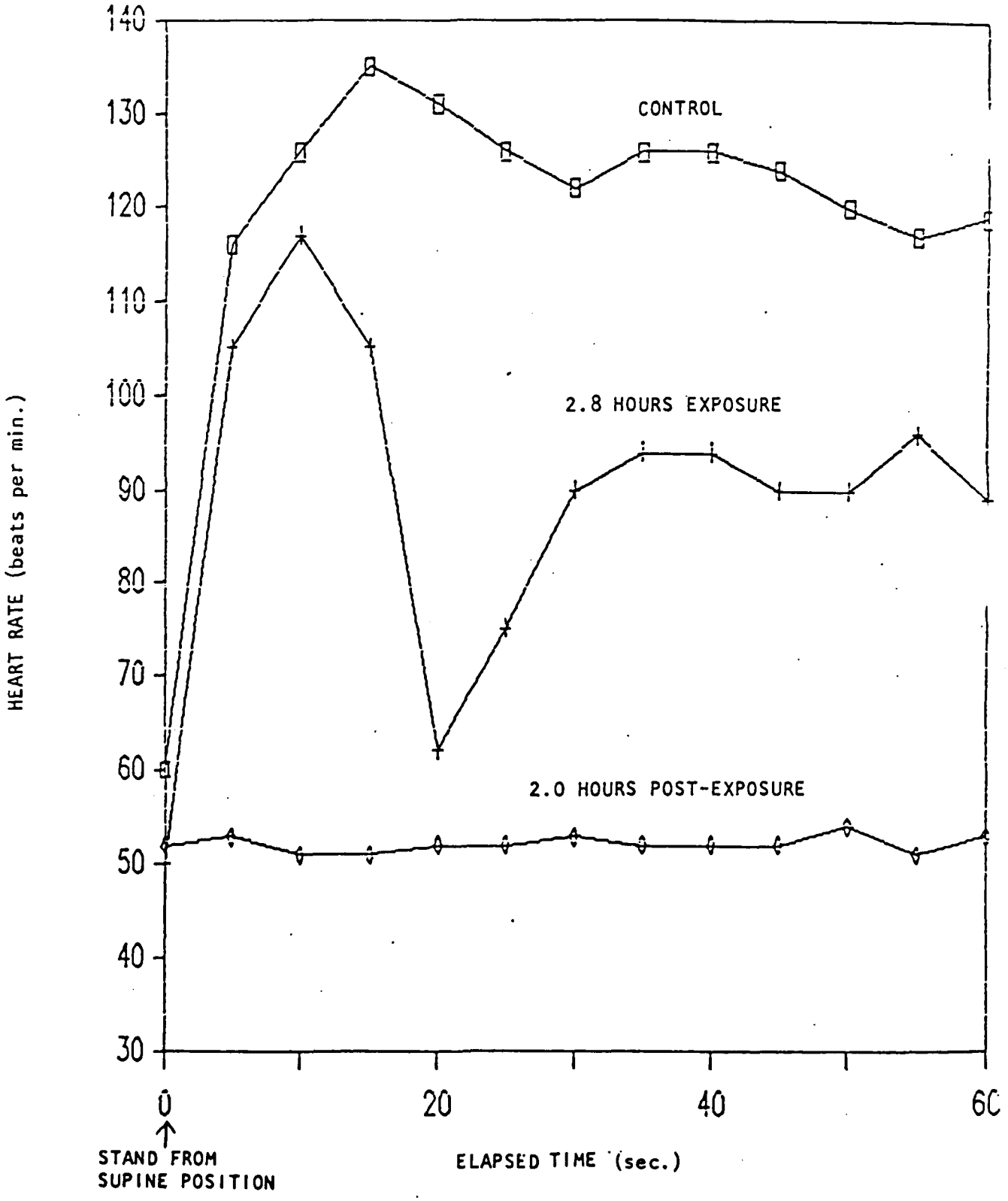


FIGURE 27.

EFFECTS OF CONTINUOUS OXYGEN EXPOSURE AT 2.0 ATA ON HEPATIC BLOOD FLOW AND FUNCTION
(INDOCYANINE GREEN DYE METHOD)

(mean values, N=5)

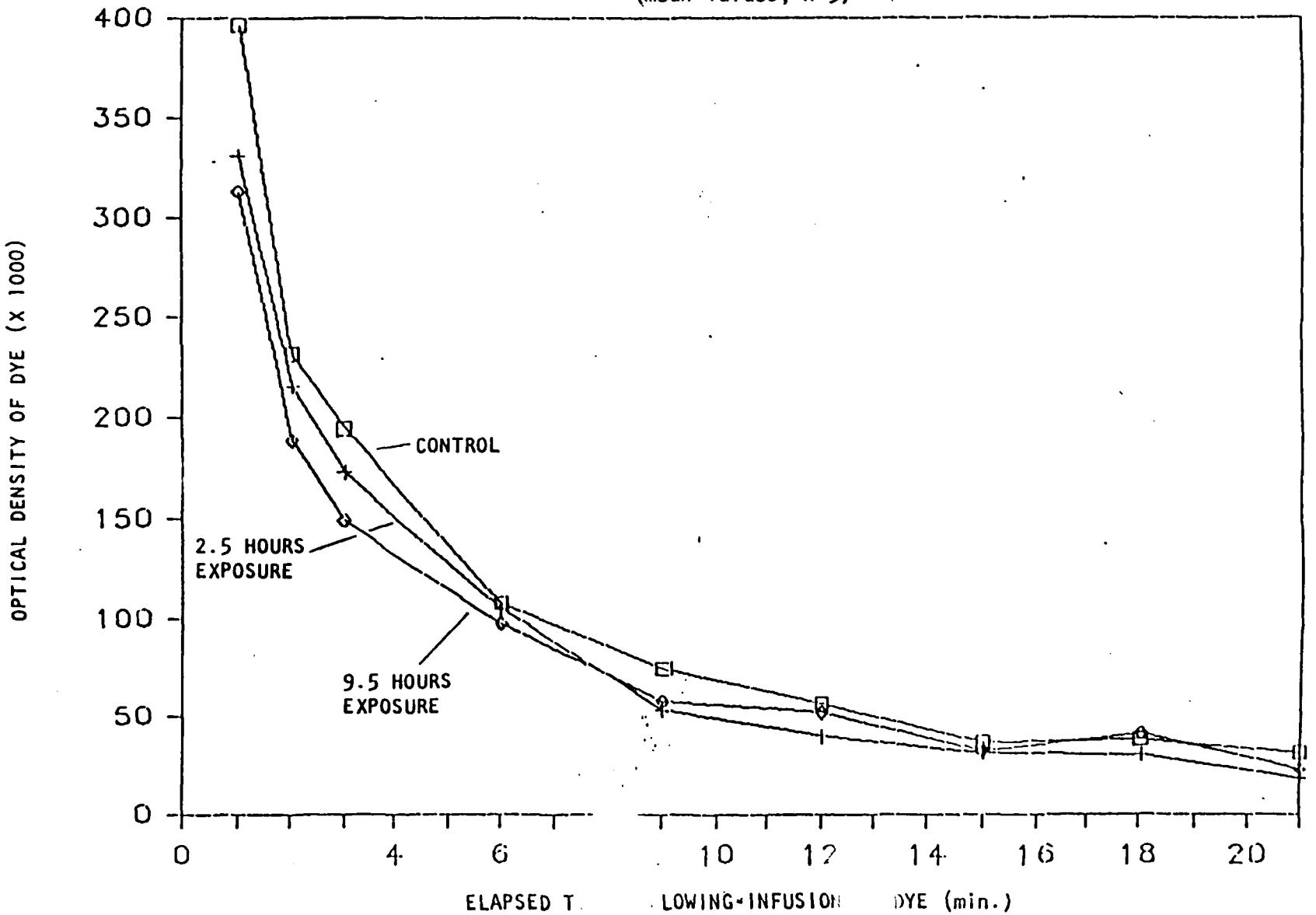


TABLE 22

HEMODYNAMIC MEASUREMENTS DURING
OXYGEN EXPOSURE AT 1.5 ATA

(Mean Values ± SD in 7 Supine Resting Subjects)

	Pre-exposure Control	Mean Exposure Time 2.2 Hours	Mean Exposure Time 16.0 Hours
Heart Rate (beats/min)	58.7 ± 15.4	57.0 ± 12.9	66.0 ± 8.2
Stroke Volume (% change)		-14.0 ± 13.9	-18.0 ± 24.0
Cardiac Output (% change)		-16.4 ± 10.1	-7.3 ± 20.6
Mean Arterial Blood Pressure (torr)	97.3 ± 9.8	89.6 ± 9.9	92.7 ± 15.6
Systemic Vascular Resistance (% change)		+12.3 ± 17.9	+11.7 ± 47.7

At 16.0 hours of exposure, stroke volume and cardiac output were still less than control levels by about 18% and 7%, respectively, with an increase in sinus node rate from 57/min. during early exposure to 66/min. Mean arterial blood pressure was still less than the control value (92.7 vs. 97.3 torr), and systemic vascular resistance remained stable at 12% above control. Again, none of the changes were statistially significant.

Responses to Active Standing. Pulse rate responses to active standing during both early and late oxygen exposure at 1.5 ATA were not detectably different from pre-exposure control responses.

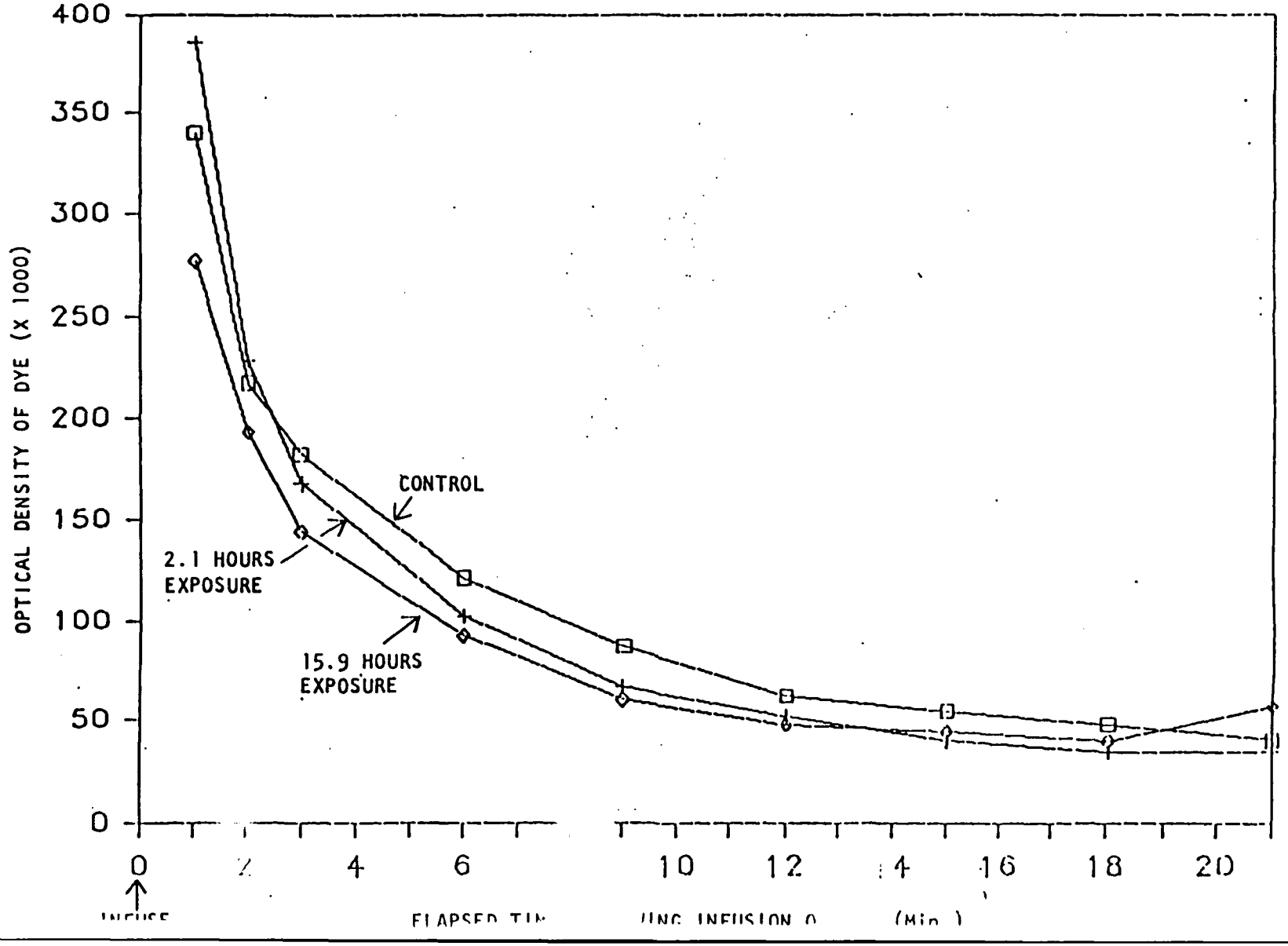
Hepatic Blood Flow and Function. Average rates of fall (N=7) in arterial dye concentration after an intravenous bolus indicate that hepatic blood flow and function at 2.1 and 15.9 hours of exposure to oxygen at 1.5 ATA were not detectably different from pre-exposure control responses (Fig. 28).

FIGURE 28.

EFFECTS OF CONTINUOUS OXYGEN EXPOSURE AT 1.5 ATA ON HEPATIC BLOOD FLOW AND FUNCTION

(INDOCYANINE GREEN DYE METHOD)

(mean values, N=7)



HEMATOLOGIC STUDIES

Complete blood cell counts, hemoglobin concentration and hematocrit determinations were performed on samples of venous blood drawn the day preceding exposure, before and after exposure, and on two consecutive days following exposure.

Results. Hematologic changes in response to O_2 breathing at 2.0 ATA and at 1.5 ATA were qualitatively similar (Fig. 29, 2.0 ATA; Fig. 30, 1.5 ATA). Both hemoglobin concentrations and hematocrits remained stable. Leucocytosis with relative neutrophilia and relative lymphopenia were observed the first post-exposure day for both the 2.0 ATA and 1.5 ATA series, followed by return to baseline levels during the following two determinations. These results can be interpreted only in the light of control measurements and full statistical analysis. Twenty-hour control exposures are scheduled to be performed later this year.

FIGURE 29.

HEMATOLOGIC MEASUREMENTS BEFORE, DURING AND AFTER OXYGEN EXPOSURE AT 2.0 ATA

(mean values ± S.D. in 7 subjects)

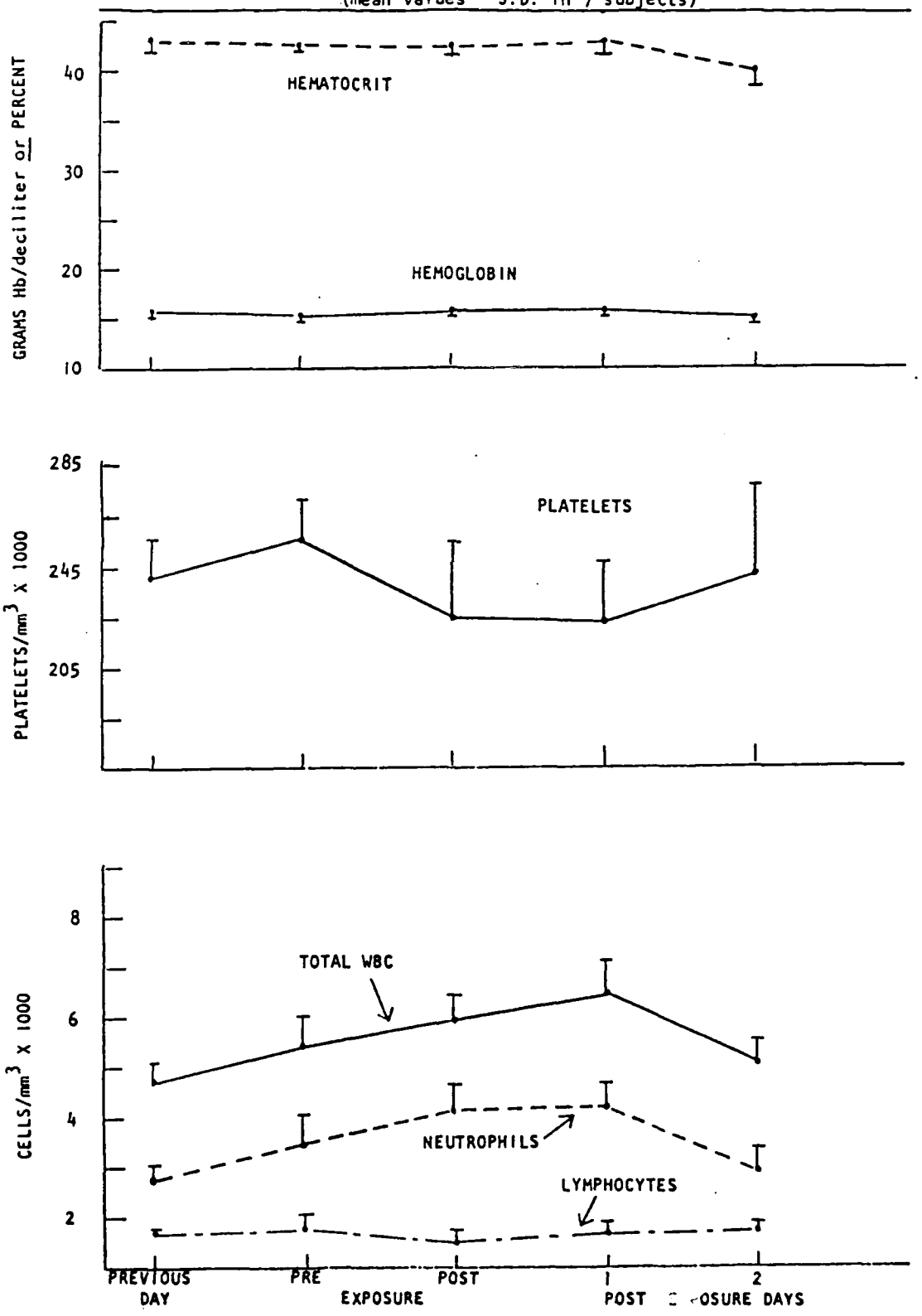
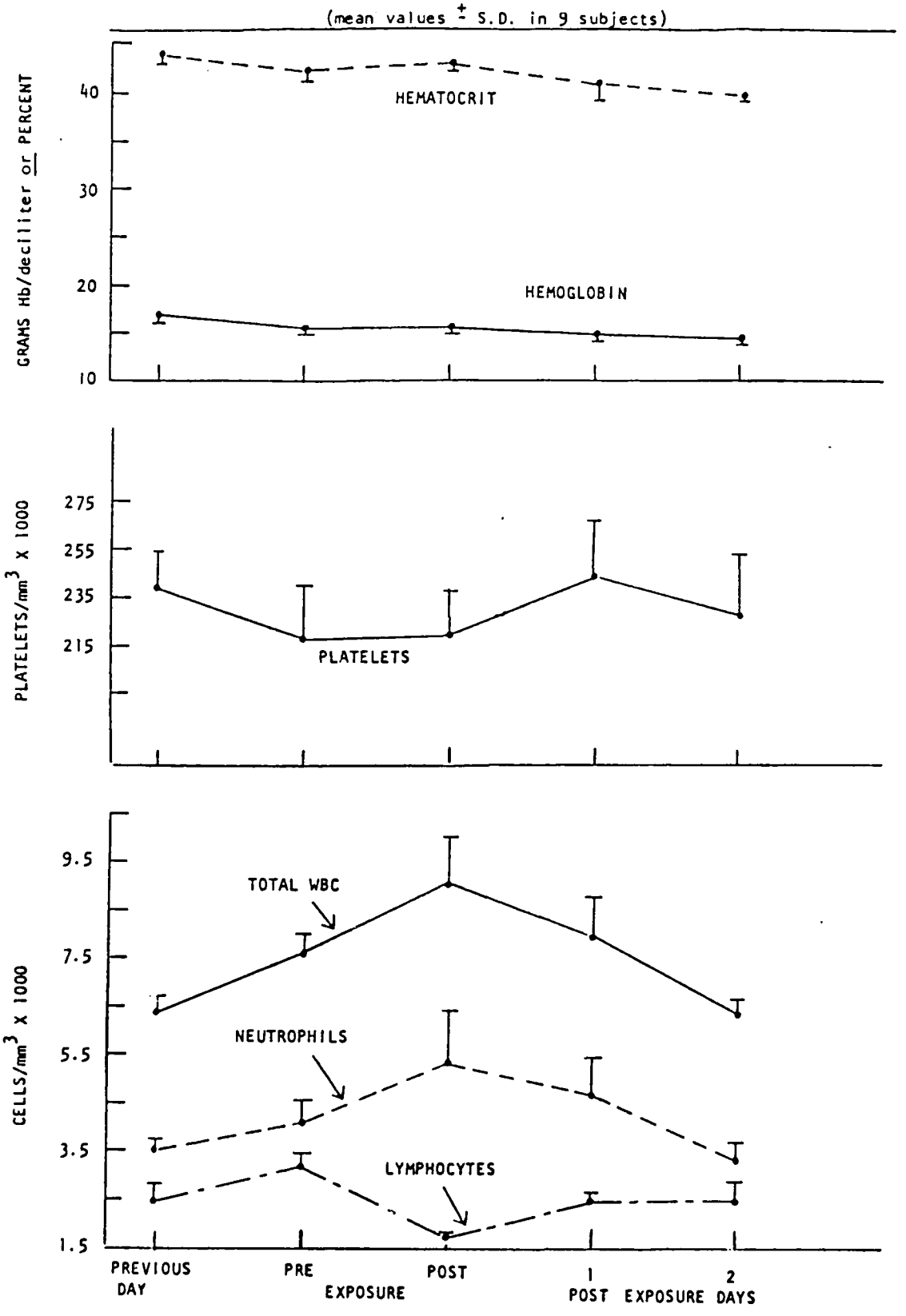


FIGURE 30.

HEMATOLOGICAL MEASUREMENTS BEFORE, DURING, AND AFTER OXYGEN EXPOSURE AT 1.5 ATA



SUMMARY OF CURRENT PROGRESS

Upon completion of experiment series at oxygen pressures of 3.0, 2.0, and 1.5 ATA, characteristic patterns of oxygen effects on specific organ stystems and functions have been defined, while other systems and functions appear to be remarkably resistant to oxygen toxicity. Results obtained to date are summarized as follows:

Brain Cortical Electrical Activity

Continuous electroencephalographic recording with scheduled periods of immobilization to assure freedom from movement artifact has shown that brain cortical electrical activity is remarkably unaffected by oxygen exposure even at 3.0 ATA for 3.5 hours. Definite EEG changes were found at 3.0 ATA in only two subjects. One had classical EEG manifestations of the seizure and post-ictal phases of a typical oxygen convulsion at 3.0 hours of exposure. No pre-convulsive EEG changes were observed. The other subject had a 7-second interval of flat EEG in association with extreme bradycardia and a 20-second period of unconsciousness immediately after a 2.5-hour exposure. Return to consciousness was accompanied by a mild clonic seizure and a 30-second interval of disorganized EEG activity, followed by resumption of normal activity. No prominent EEG changes were observed during 8-12 hour exposures at 2.0 ATA and 16-19 hour exposures at 1.5 ATA. Detailed analysis of the EEG records obtained at 2.0 and 1.5 ATA is not yet complete.

Effects on Visual Function

Oxygen Exposure at 3.0 ATA. Loss of peripheral vision starting at about 2.5 hours of exposure in most subjects was a consistent finding. Average visual field decrement upon exposure termination at 3.5 hours was 50% of the normal area, with four subjects losing 80-90% of the visual field area. Essentially complete recovery of visual fields occurred within 30 minutes of exposure termination in those subjects who had frequent post-exposure measurements.

Of the fourteen subjects who completed 3.5 hours of oxygen exposure at 3.0 ATA, only three had definite ERG changes (reduction in amplitude of b-wave). Full recovery occurred within 20-24 hours after exposure termination, but no ERG measurements were made during the 3-20 hour post-exposure interval.

Oxygen Exposure at 2.0 ATA. Visual field areas were definitely reduced in one subject (-35%) and possibly reduced in another (-15%) of the seven subjects who breathed oxygen at 2.0 ATA for 8-12 hours. In marked contrast to the rapid recovery observed at 3.0 ATA, however, there was no recovery at 2.2 hours after exposure termination and a slight residual deficit (-20%) in one eye at 10.5 hours post-exposure.

Unexpectedly, relative amplitude of the ERG b-wave was reduced on the average to half of its control level for all four subjects in whom ERG was measured during the early post-exposure interval. Two of these subjects had normal visual fields near the end of oxygen exposure. Recovery of ERG within 12-16 hours post-exposure was documented in three of the four subjects.

Oxygen Exposure at 1.5 ATA. Loss of peripheral vision did not occur in any of the nine subjects who breathed oxygen at 1.5 ATA for 16-19 hours, and only one subject had a decrement in amplitude of the ERG b-wave. Recovery of b-wave amplitude in this subject was noteworthy in that it required more than 2.4 days after exposure termination. Complete recovery was documented at 4.5 days post-exposure.

Location of Oxygen Effect on Vision. Results to date provide no evidence for an oxygen effect on central vision. Neither visual acuity nor the visual evoked cortical response, which are measures of central visual function, have been consistently affected by oxygen exposure. Visual indices which have been affected, visual fields and the ERG, are both determined primarily by peripheral vision. The observation at 3.0 ATA that visual field decrements occur earlier and more consistently than ERG changes is consistent with evidence in other clinical states that visual field area is altered before ERG changes occur. During oxygen exposure at 2.0 and 1.5 ATA, however, amplitude of the ERG b-wave was reduced in a total of three subjects who had normal visual fields. Determination of the basis for this reversal in relative sensitivity may provide insight regarding possible mechanisms for oxygen effects on the retina.

Although visual field decrements observed during oxygen exposure at 3.0 ATA were much greater than those found at 2.0 ATA, reversal upon exposure termination occurred much more rapidly after exposure at 3.0 ATA. The slower rate of recovery for visual fields at 2.0 ATA (and for the ERG b-wave at 1.5 ATA) may be related to the fact that these functional deficits were sustained for a much longer period of oxygen exposure than they were at 3.0 ATA. Depletion of critical enzyme reserves or recovery processes are possible mechanisms for such an effect.

Auditory-Vestibular Function

Oxygen exposure at 3.0 ATA for 3.5 hours had little or no effect on auditory-vestibular function. Even the subject who convulsed at 3.0 hours performed well on a high frequency hearing test given just a few minutes before his seizure. Analysis of the measurements obtained during and after the much longer exposures at 2.0 and 1.5 ATA is still in progress.

Mental and Psychomotor Function

The selected measures of mental and psychomotor function have remained remarkably stable under all conditions of oxygen

exposure that have been studied to date. Comparisons of mental and psychomotor performances during oxygen exposure at 3.0 ATA and air exposure at 1.0 ATA indicate that learning trends evident during air exposure may have been masked or eliminated during oxygen exposure. Similar comparisons will be performed with the results obtained during much longer exposures at 2.0 and 1.5 ATA when data from 20-hour air exposures at 1.0 ATA are available.

Respiratory Function and Gas Exchange

Respiratory Measurements. Results obtained during oxygen exposure at 3.0 ATA showed the expected early onset of increased pulmonary ventilation with concurrent decrement in end-tidal PCO_2. These alterations remained stable throughout the 3.5-hour exposure in most subjects. However, the subject who convulsed had distinct changes in his ventilatory pattern that started about 40 minutes before seizure and became rapidly progressive. The alterations included an increase in expiratory time with reciprocal decrease in breathing rate, reduction in pulmonary ventilation, and increase in end-tidal PCO_2. His normal breathing pattern was resumed within one hour after seizure.

Ventilatory measurements obtained during the much longer oxygen exposures at 2.0 and 1.5 ATA have not been fully analyzed. Preliminary analysis indicates the occurrence of periodic breathing in some subjects, particularly during the 16-19 hour exposures at 1.5 ATA.

Gas Exchange. Respiratory exchange ratio (R) at rest was not altered after oxygen exposure at 3.0 ATA for 3.5 hours. After breathing oxygen at 2.0 ATA for 8-12 hours, R was significantly reduced at rest, but not during mild exercise. After oxygen exposure at 1.5 ATA for 16-19 hours, R was reduced both at rest and during mild exercise. Analyses of gas exchange ratios during oxygen breathing at 2.0 and 1.5 ATA have not yet been completed.

Effects on Body Temperature

Measurements of rectal temperature in subjects exposed to oxygen at 3.0 ATA for 3.5 hours show the apparent onset of a decline near the end of the exposure. The subject who convulsed had a greater than average rate of fall in rectal temperature prior to his seizure. Rectal temperature measurements during oxygen exposure at 2.0 and 1.5 ATA have not yet been analyzed completely.

Pulmonary Effects

Oxygen exposure at 3.0 ATA for 3.5 hours had statistically significant effects on pulmonary function, but the functional alterations were not prominent and were not associated with severe symptoms. All functional decrements were fully reversed by the day after exposure. In contrast to the relatively mild

effects on pulmonary function caused by oxygen exposure at 3.0 ATA to the limits of CNS tolerance, durations of oxygen exposure at 2.0 and 1.5 ATA in 15 of 16 subjects were limited by severity of pulmonary symptoms and decrement in pulmonary function. Comparative average percent changes in FEVC with respect to pre-exposure control values were: -3.4% after 3.5 hours at 3.0 ATA (N=13), -18.8% after 8-12 hours at 2.0 ATA (N=7), and -19.7% after 16-19 hours at 1.5 ATA (N=9).

Lung Volumes and Flow Rates. Both inspiratory and expiratory lung volumes and flow rates were significantly reduced after oxygen exposure at each of the pressures that have been studied to date. They also appear to provide the best available indices of rate of pulmonary intoxication during continuous oxygen exposure. Complete recovery of lung volumes and flow rates occurs within one to four days post-exposure. Starting from equivalent degrees of lung volume decrement, rate of recovery after oxygen exposure at 1.5 ATA appears to exceed that which occurs after exposure at 2.0 ATA.

Density Dependence of Flow Rates. Although measurements in five subjects indicated that $\Delta\dot{V}max_{50}$ was reduced after oxygen exposure at 3.0 ATA for 3.5 hours, no significant changes were found after much longer exposures at 2.0 or 1.5 ATA. Detailed analysis of individual data may reveal the basis for this apparent discrepancy.

Closing Volumes. No significant changes in closing volumes were found after oxygen exposures at 3.5, 2.0, or 1.5 ATA. However, average data indicate that CV may be increased after exposure at 2.0 or 1.5 ATA and then return to pre-exposure control levels over a 7 to 11-day post-exposure interval.

Carbon Monoxide Diffusing Capacity. In agreement with previous data (14), D_{LCO} was significantly reduced after oxygen exposure at 2.0 ATA, and it was also reduced after prolonged exposure at 1.5 ATA. The observation that D_{LCO} was not reduced after oxygen exposure at 3.0 ATA for 3.5 hours indicates that oxygen effects on the alveolar-capillary membrane occur later than effects on lung volumes and flow rates during the progression of pulmonary intoxication at that pressure. Of all pulmonary function indices that are known to be affected by oxygen to date, repeated post-exposure measurements of D_{LCO} appear to provide the best index of complete recovery from pulmonary intoxication, since it was significantly reduced for at least 9 days after oxygen exposure at 2.0 ATA.

Lung Compliance. Static lung compliance was significantly reduced after oxygen exposure at 2.0 ATA. Average values of C_L were also reduced after exposure at 1.5 ATA, but the change was not statistically significant. Dynamic lung compliance at breathing rates of 15, 30, and 60 was not reduced after oxygen exposure at 1.5 ATA.

Airway Resistance. No changes in airway resistance have been detected after oxygen exposures at 3.5, 2.0, or 1.5 ATA.

Arterial Blood Gases and Acid-Base State. No changes in $(A-a)\Delta PO_2$ and acid-base state at rest or during mild exercise were detected after oxygen exposure at 2.0 or 1.5 ATA. Measurements of $(A-a)\Delta PO_2$ during oxygen breathing were consistent with production of alveolar atelectasis by prolonged oxygen exposure in only one of four subjects at 2.0 ATA and in one of six subjects at 1.5 ATA.

Bronchoalveolar Lavage. Results of initial analyses indicate that a relative alveolar polycytosis persists for at least 8 to 10 hours after oxygen exposure at 2.0 or 1.5 ATA. More comprehensive analyses will be performed after completion of control lavage procedures.

Effects on Cardiocirculatory Functions

Oxygen effects on cardiocirculatory functions appear to be characterized by nearly immediate onset of an inhibitory influence that persists throughout oxygen exposure and, during exposures that are continued for more than 4 to 5 hours, has excitatory phenomena superimposed upon it.

Oxygen Exposure at 3.0 ATA. Only inhibitory effects were observed at 3.0 ATA. These were manifested by persistent decrements in sinus node discharge rate of varying intensity in different individuals. Sinus pauses with inhibition of normal escape mechanisms occurred in some individuals. These depressive influences did not interfere with performance in most cases, but one subject had transient loss of consciousness following a 13-second sinus pause at 2.5 hours of oxygen exposure.

Oxygen Exposure at 2.0 ATA. Magnitude of inhibitory effects at 2.0 ATA was less than that observed at 3.0 ATA. After 4 to 5 hours of exposure, inhibitory effects were masked by progressive acceleration of sinus pulse rate with concurrent decrements in the incidence of sinus arrhythmia and periods of nodal control. Despite the excitatory phenomena, persistence of an inhibitory influence was manifested in one subject by inhibition of pulse rate acceleration upon standing.

Oxygen Exposure at 1.5 ATA. Depression of sinus node discharge rate was not observed even during early oxygen exposure at 1.5 ATA. In addition to progressive acceleration of sinus pulse rate after 4 to 5 hours of exposure, premature atrial and ventricular activity developed. Progressive ectopic ventricular activity became so prominent in one subject that his oxygen exposure was terminated at 17.7 hours prior to a pulmonary endpoint.

Hepatic Blood Flow and Function. Rates of indocyanine green dye clearance from the arterial circulation after intravenous

injection were not altered during early and late oxygen exposure at 2.0 or 1.5 ATA. This indicates that hepatic blood flow and function, as evaluated by this method, were not detectably affected by oxygen exposures that approached the limits of pulmonary tolerance.

PUBLICATIONS RESULTING FROM PROGRAM

Lambertsen, C.J., J. Clark, R. Gelfand, J. Pisarello, R. Jackson, R. Marsh, W. Cobbs, R. Harner, J. Bevilaqua, D. Fletcher, and D. Montabana. Predictive Studies V - "Tolerance of human organs and functions to continuous hyperoxia." Undersea Biomed. Res. 11(1)-Supple.: 34, 1984.

Clark, J., C.J. Lambertsen, J. Pisarello, R. Jackson, and R. Gelfand. Cardiopulmonary effects of continuous O_2 exposure at 3.0 ATA for 3.5 hours in man. Undersea Biomed. Res. 11(1)-Supple.: 29, 1984.

Fletcher, D.E., R. Gelfand, C.J. Lambertsen, J. Clark, and J. Pisarello. Effects on human abilities of continuous O_2 exposure at 3.0 ATA for 3.5 hours. Undersea Biomed. Res. 11(1)-Supple.: 34, 1984.

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Gelfand, R., J.M. Clark, C. Lambertsen, R. Jackson, and J. Pisarello. Hyperoxia at 3.0 ATA for 3.5 hours (in Predictive Studies V). Effects on ventilatory parameters. Undersea Biomed. Res. 12(1)-Supple.: 19,20, 1985.

Marsh, R.R., C.J. Lambertsen, D.M. Schwartz, and J.M. Clark. Auditory and vestibular function in hyperbaric oxygen. Otolaryngology 93(3): 390-393, 1985.

ABSTRACT OF PROGRESS

During the present year, 16 subjects were studied before, during, and after O_2 exposure: seven at 2.0 ATA (8-12 hours) and nine at 1.5 ATA (16-19 hours). Endpoints of exposure were determined by progressive pulmonary intoxication in 15 subjects, and by progressive cardiac ectopic ventricular activity in one subject at 1.5 ATA. Extensive data were obtained with important findings of both effect and absence of effect of these exposures on numerous functions and organ systems including spontaneous CNS electrical activity, visual and auditory/vestibular systems, perceptual and cognitive functions, pulmonary and respiratory systems, hepatic and hematologic function.

4. METHODS

General Concept and Approach

The present plans for carrying out the overall Program are those described in the initial proposal. Sequences of exposures to the pressures selected for investigation have been adjusted as new information obtained made this sensible. For example, in the course of developing the necessary instrumentation systems and procedures, preliminary oxygen exposure experiments indicated lack of early or prominent central nervous system symptoms at 2.0 ATA. This led to an early change in plan, to allow determinations at the highest pressure (3.0 ATA) of the nature of toxic neurological effects to be expected and sought for. When initial, two hour, exposures at 3.0 ATA showed no definitive changes, plans were made and approved to extend exposure durations at each oxygen pressure (1.5, 2.0, 2.5, 3.0 ATA)[1]. On the other hand, the original plan to complete the 3.0, 2.0 and 1.5 ATA exposures first, and to incorporate the results of these phases into planning the critical exposures at 2.5 ATA remains sensible and is being followed. Methods for the forthcoming exposures at 2.5 ATA will make extensive use of the information and experience obtained during the prior exposure phases. The normal Institute Predictive Study procedure will be used for termination of exposure by the designated safety officer at any point prior to the approved maximum exposure as guided by criteria involving changes in the EEG, pulmonary function, cardiac function, respiratory pattern and function, end-tidal CO_2, and body temperature.

The IFEM "Predictive Study" principle of using repetitive modules of multiple specific measurements by multiple collaborating investigators will be continued, as practical, to seek rates of development of (and recovery from) detectable effects. Modular measurements performed during O_2 exposures will be supplemented by "before and after" measurements when necessary.

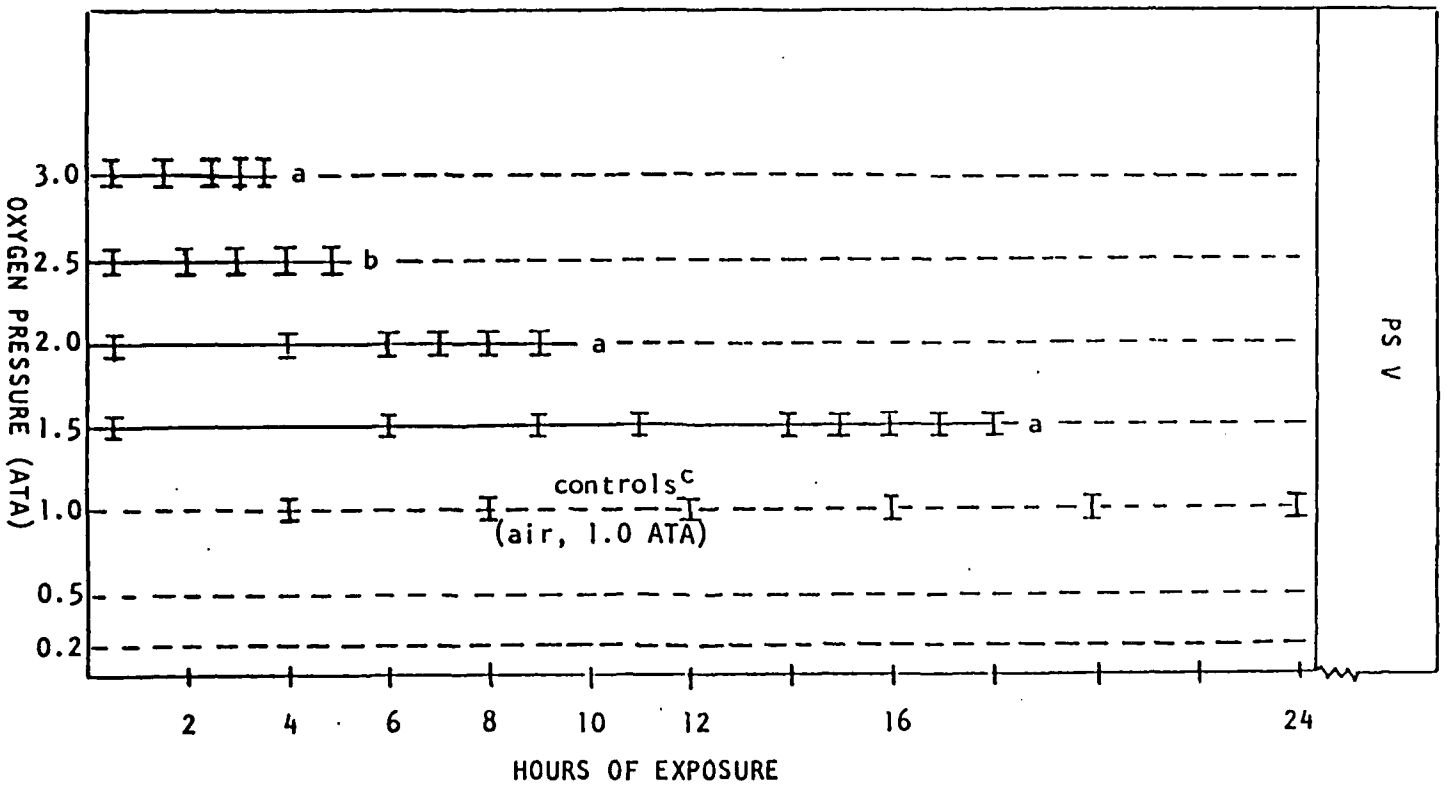
Subjects and Exposures

Because of the extended, several-year period required for even the continuous O_2 exposure phases (Fig. 31) of the large overall program, and the inadvisability of shifting a subject from one oxygen pressure to another until more information is obtained concerning the nature of oxygen effects, it has not yet been practical to study each subject fully at each planned exposure pressure. It is anticipated that the subjects in the air-control series for the 2.0 and 1.5 ATA exposures will be from the groups employed for those exposures. Of the subjects who participated in the 3.0 ATA phase, one each participated in the 2.0 ATA series and the 1.5 ATA series. When practical, subjects from the latter phases will be recruited for the 2.5 ATA phase. As understanding of effects has been improved, specific changes in patterns of exposure and measurements have been used to improve precision.

[1]See Page 16 for approved extended exposure times.

FIGURE 31.

HUMAN CONTINUOUS 100% OXYGEN EXPOSURE CONDITIONS
(PREDICTIVE STUDIES V)



a. Exposures completed as Phases of PS V.

b. Phase at 2.5 ATA to be accomplished in the coming year.

c. Control series at 1.0 ATA for the 3.0 ATA Phase completed.
Control series at 1.0 ATA for the 1.5 and 2.0 ATA Phases to be done this year.

Scope of Measurements

Table 23 cites specific projects and measurements now in progress and planned for the Program year ahead. It is recognized that these projects do not encompass the entire scope of the Continuous Oxygen Tolerance Predictive Study V, as conceived and planned by this Institute. Even at this stage in the Predictive Study the extensive existing program is still not optimally supported, and still depends heavily upon recruitment of unpaid scientific and technical experts for performance (see Budget, First Twelve Months). This situation handicaps the overall Program, but allows for full quality in the specific projects selected. If additional funds become available, from any source, it will be possible to extend the Program scope, and to assure continuity of the required investigative skills.

Extension of scope had been planned in detail as part of the overall Program Plan. It included study of specific additional target organ systems now being investigated in animals and as tissues (blood, renal and electrolyte system, and liver). It additionally includes expanded study of oxygen effects upon heart, visual system, mental function and respiratory system (21,22,23,25).

Specific Measures - 2.0, 1.5 and Planned 2.5 ATA Exposures

Each measurement, on functions within the Collaborative Predictive Study Program scope, is performed by an investigator with scientific and technical expertness for the specific function. The following are brief descriptions of major aspects of measurement.

Electroencephalogram. Recording on Grass EEG machine and on magnetic tape, from 18 electrodes placed by measurement according to the International 10-20 System, with on-line direct visualization and energy spectrum analysis. Specific periods of "EEG Quiet" in each Module for Photic Stimulation and Eyes-Open/Eyes-Closed recording. Clinical laboratory EEG workup as control and medical evaluation; post-exposure examination when indicated.

Hearing and Vestibular Functions. High frequency air conduction audiogram over frequencies of 8,000 to 20,000 Hz, using Demlar Extended High Frequency Audiometer during exposure. Complete audio/vestibular/evoked response workup before and after exposure. Cortical Evoked Potential measurement during exposure.

Visual Functions. Visual Evoked Potential by checkerboard pattern reversal at a rate of two reversals per second. Electroretinogram by strobe flash in a Ganzfeld Full-Field Stimulator and corneal electrodes (Burian-Allen), with one eye dark-adapted and one not. Visual fields by Rodenstock Projection Perimeter. Complete workups before and after exposures.

TABLE 23.

SCOPE OF PROGRAM PLAN FOR ORGAN AND FUNCTION MEASUREMENTS DURING CONTINUOUS OXYGEN EXPOSURE IN MAN*

Electroencephalography
- Clinical Interpretation
- On-line Spectral Analysis
- Response to Photic Stimulation

Visual Function
- Visual Evoked Cortical Potential Response
- Electroretinography (Dark and Light Adapted)
- Fields (Goldman Perimetry)
- Pupillary Reaction
- Acuity
- Accommodation
- Color Vision

Auditory/Vestibular Function
- Audiometry (Air Conduction)
- Brainstem Auditory Evoked Response
- Cortical Auditory Evoked Response
- High Frequency Audiography
- Eye Tracking, Nystagmography
- Caloric Stimulation, Postural Balance

Muscle Power (Skeletal, Respiratory)

Performance (Perceptual, Cognitive, and Psychomotor)

Pulmonary Function
- Flow-Volume Loops (Forced Vital Capacity)
- Density Dependent Flow Rates (Inspiratory, Expiratory)
- Closing Volumes
- Peak Inspiratory and Expiratory Pressures
- Airway Resistance and Conductance
- Frequency Dependence of Compliance
- Carbon Monoxide Diffusing Capacity of Lung
- Arterial Blood Gases and Acidity (PCO_2, PO_2, pH)

Cellular and Chemical Composition of Bronchoalveolar Lavage Fluid

Respiration/Respiratory Gas Exchange/Metabolism

Temperature Regulation

Cardiovascular Function
- Electrocardiography
- Cardiac Output, Rate, Stroke Volume
- Mean Thoracic Impedance
- Blood Pressure, Systemic Vascular Resistance
- Orthostatic Reflex Responses

Liver Blood Flow and Function

Endocrine Activity, via Plasma Hormone Levels

Insulin	Vasopressin	Adrenocorticotropic Hormone
Cortisol	Growth Hormone	Thyroid Stimulating Hormone
Aldosterone	Beta-Endorphin	

NOTE* Programmed sequence of sampling and measurements during an exposure of each subject is carried out in accordance with a fixed modular procedure, repeating the specific measures throughout the period of continuous hyperoxia. Frequency of modular measurements, and duration of overall exposure is determined by oxygen pressure level being studied.

Cardiac Functions. Electrocardiography, with on-line display and magnetic tape recording. Impedance measurement of cardiac stroke volume (Minnesota Impedance Cardiograph). Circulatory reflex responses on change from supine to quiet standing position. Blood Pressure.

Pulmonary Functions. Flow-volume loops (forced vital capacity and multiple other measures from this maneuver), and slow vital capacity, by computerized spirometer during exposures. Repeated pulmonary workups before exposure for controls, and extended followup to recovery post-exposure including Single Breath CO diffusing capacity, Flow-Volume loops (including density dependence with He/O_2), Slow Vital Capacity, Closing Volume, and Body Box measurements of lung volume, airway resistance, compliance, frequency dependence of compliance and pulmonary resistance. These measures include those described for prior IFEM Pulmonary O_2 Toxicity Studies (5,13,14).

Cognitive/Psychomotor Measurements. Tests are administered, scored and analyzed by the computer-controlled Performance Measurement System (PMS) developed at IFEM from the original Navy SINBAD concept. Subjects are trained to stability, over days prior to experiment. Test sequences are incorporated into the measurement modules, for repetitive use before, during and after oxygen exposure. Test battery before and after oxygen exposure is more extensive than, but includes the short sequences useful within the complex measurement module. For the oxygen breathing periods the following are used: Short Term Memory, Reasoning Ability, Visual Reaction Time and Finger Dexterity. As positive information develops, more specific studies of performance will be conducted.

Respiratory Functions

During exposures, inspiratory flow is monitored, and is recorded on magnetic tape for analysis of respiratory functions including respiratory patterns and timing. Gas collection is during quiet periods of EEG measurements, for ventilatory/gas exchange and end-tidal CO_2 measurement. Pre-exposure and post-exposure measurements of ventilatory response to progressive hypoxia (end-tidal CO_2 held constant) and for ventilatory response to CO_2 (rebreathing method) are obtained.

Continuous On-Line Monitoring

Parameters continuously monitored for subject safety include EEG as required, EKG (patient monitor with alarms), instantaneous bradycardia detector with alarm, inspiratory flow (breath-by-breath) including visual monitoring on oscilloscope, end-tidal PCO_2, and body temperature. In addition, the O_2 concentration in the subject's oro-nasal mask is continuously monitored to assure adequacy of mask emplacement, absence of leakage, and patency of one-way valves.

Particular Problems of Method

The long experiment durations for the lower O_2 pressures created requirements for control which must be considered part of the oxygen study, but which have relevance to chamber studies for other purposes. Feeding, fluid balance and waste elimination have been resolved, as were provisions for rest and sleep. These factors and their resolution will become even more important as the Program evolves into intermittent O_2 exposures for determinations of CNS O_2 Tolerance Extension.

From the beginning of the Program, a primary problem was a lack of certain critical equipment and the need to borrow key items, with daily return to priority clinical functions. Failure to receive requested equipment support via the special 1984 DOD Instrumentation Grant Program administered by ONR left the Program in its early stages not in full control of schedule of experiments involving large numbers of specialized investigators. Requirements for vital equipment have, for present purposes, largely been met through acquisition at low cost and skillful adaptation of used and even outmoded equipment, effective maintenance of aged equipment, and continued loan of some items. Assistance is still needed to stabilize the availability of key instruments over the remaining periods of Predictive Study V and VI.

A major requirement in staff has been that of a trained EEG Technician, to assist in all aspects of CNS and Sensory recording, including EEG, Evoked Potentials, ERG and Audiographic measurements. Success in these areas has been accomplished to date by obtaining services of an EEG technician for electrode application only, and by extreme dedication of the resident PS-V investigators in each performing multiple functions.

Electroretinography continues to be technically challenging. However, change from a Dawson thread to a Burian-Allen contact lens electrode, and extensive experience in its use, has greatly improved reliability and reproducibility.

Data Analysis

The principle of the Program involves use of each subject as his own control. For such study within a subject repetitive measurements are made during a control phase as a baseline for changes induced by oxygen, and for determinations of rate of recovery. Each subject therefore serves as his own control for each particular oxygen pressure to which he is exposed.

Where subjects are in fact exposed to more than one oxygen pressure, analysis will take this into account. Where necessary, comparisons will be made of populations of subjects exposed at different pressures, as was done for the Institute analysis of human pulmonary oxygen tolerance (4,24) using regression analysis to derive the desired tolerance curves.

Analysis of data for each individual subject will include comparison and correlation of oxygen effects on different organ systems and functions during both the development of oxygen poisoning and recovery from its toxic effects. When data are available for the same subject at more than one oxygen pressure, similar analyses will be performed over the entire range of pressures to facilitate interpolation and prediction of oxygen effects at pressures that were not studied directly.

Appropriate analytical methods will be used to correlate oxygen effects on different organ systems within each group of subjects at each oxygen pressure and across a range of pressures. Group data will also be used to assess variability of individual responses to hyperoxia. Oxygen tolerance tables for specific organs and functions, and predictive curves such as those shown in Fig. 1 will be developed by integration and incorporation of all available data. The volume and diversity of the data that have been collected combine to require greater expenditure of man-years of effort to accomplish the overall task of data analysis and application than were required for actual performance of the experiments.

RELATION TO OTHER CURRENT AND PLANNED IFEM OXYGEN STUDIES

Two key areas of research are fundamental to Predictive Study V (Human Tolerance to Continuous O_2 Exposure) and its planned Predictive Study VI sequel (Extension of Human CNS and Pulmonary Oxygen Tolerance by Intermittent Exposure).

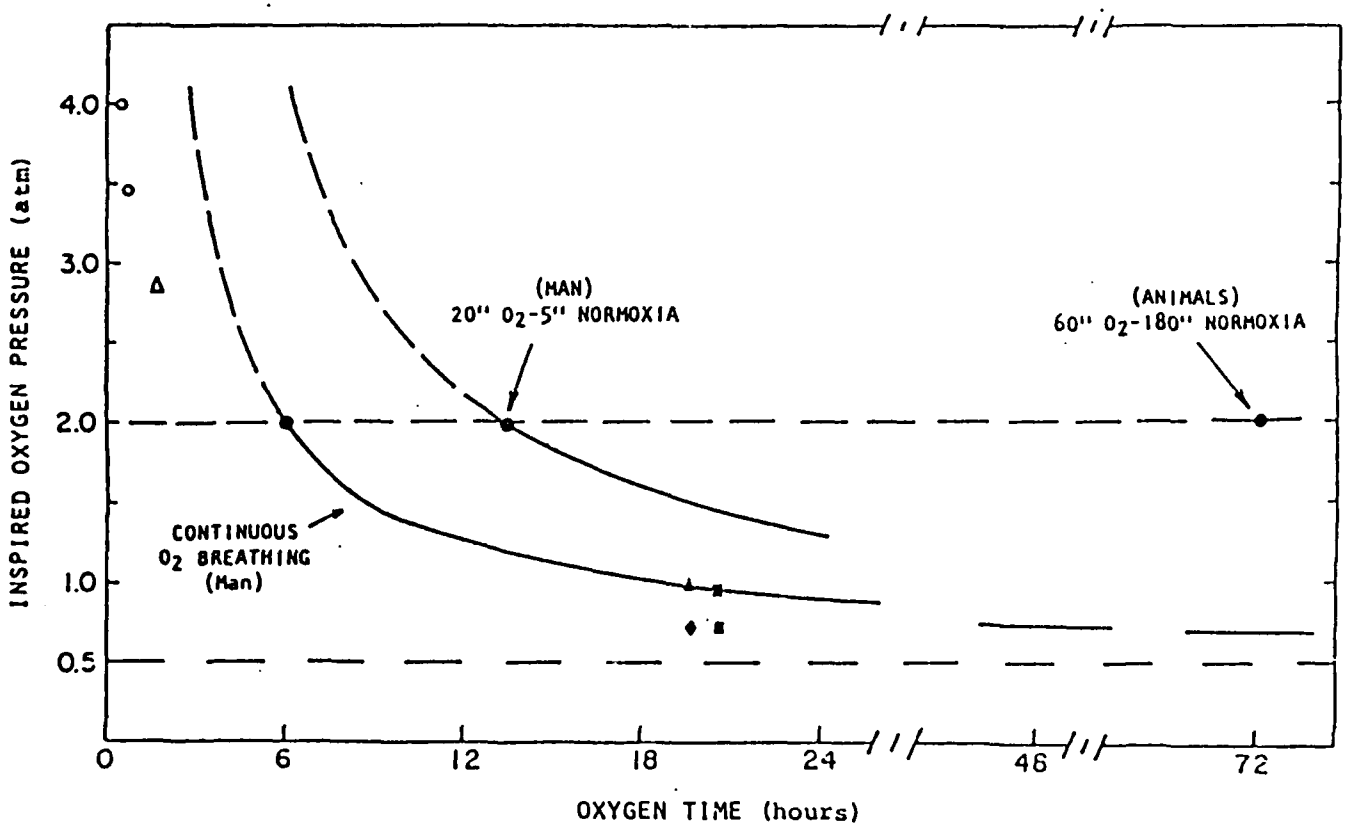
The supporting areas are (a) the basic, ONR-supported project concerning mechanisms and rates of development of oxygen toxicity in animal organs, and (b) the proposed continuation of IFEM applied research in optimal extension of oxygen tolerance in animal organs by systematic interruption of hyperoxic exposure at various pressures.

Together these interrelated investigations provide the definite promise of gross and useful extension of oxygen tolerance such as is indicated by Fig. 32. The figure shows that brief interruption of oxygen exposure at 2.0 ATA doubles human oxygen tolerance (19), and that more prolonged interruption in animals allows the equivalent of three days of oxygen exposure a 2.0 ATA with no evidence of pulmonary or CNS oxygen poisoning. (Unpublished observations, this laboratory.)

Together these complementary basic and applied projects, and the methods they involve, represent a major component of U.S. Naval-oriented oxygen tolerance research and applications.

FIGURE 32.

EFFECT OF INTERMITTENT OXYGEN BREATHING
ON PULMONARY OXYGEN TOLERANCE LIMITS IN MAN AND ANIMALS



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